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(54) **PROBES FOR DETECTING IMMUNE-RELATED GENE POLYMORPHISMS AND APPLICATIONS OF THE SAME**

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Polymorphism detection probes that can distinguish polymorphisms that have only one different base are provided. At least one oligonucleotide selected from the group consisting of the oligonucleotides of SEQ ID NOS. 4, 23, 30, 47, 57 and 64 is used as a probe in a Tm analysis. A Tm analysis using such probes allows easy detection of specific polymorphisms of the FCGR3A gene, the FCGR2A gene, the IL-10 gene, the TNF α gene and the TNF β gene that have an effect on the pharmaceutical effects of antibody drugs or the like. Moreover, such probes allow detection of two or more types of polymorphisms in a single reaction system by introducing two or more types of the probes concomitantly.

9 Claims, 3 Drawing Sheets

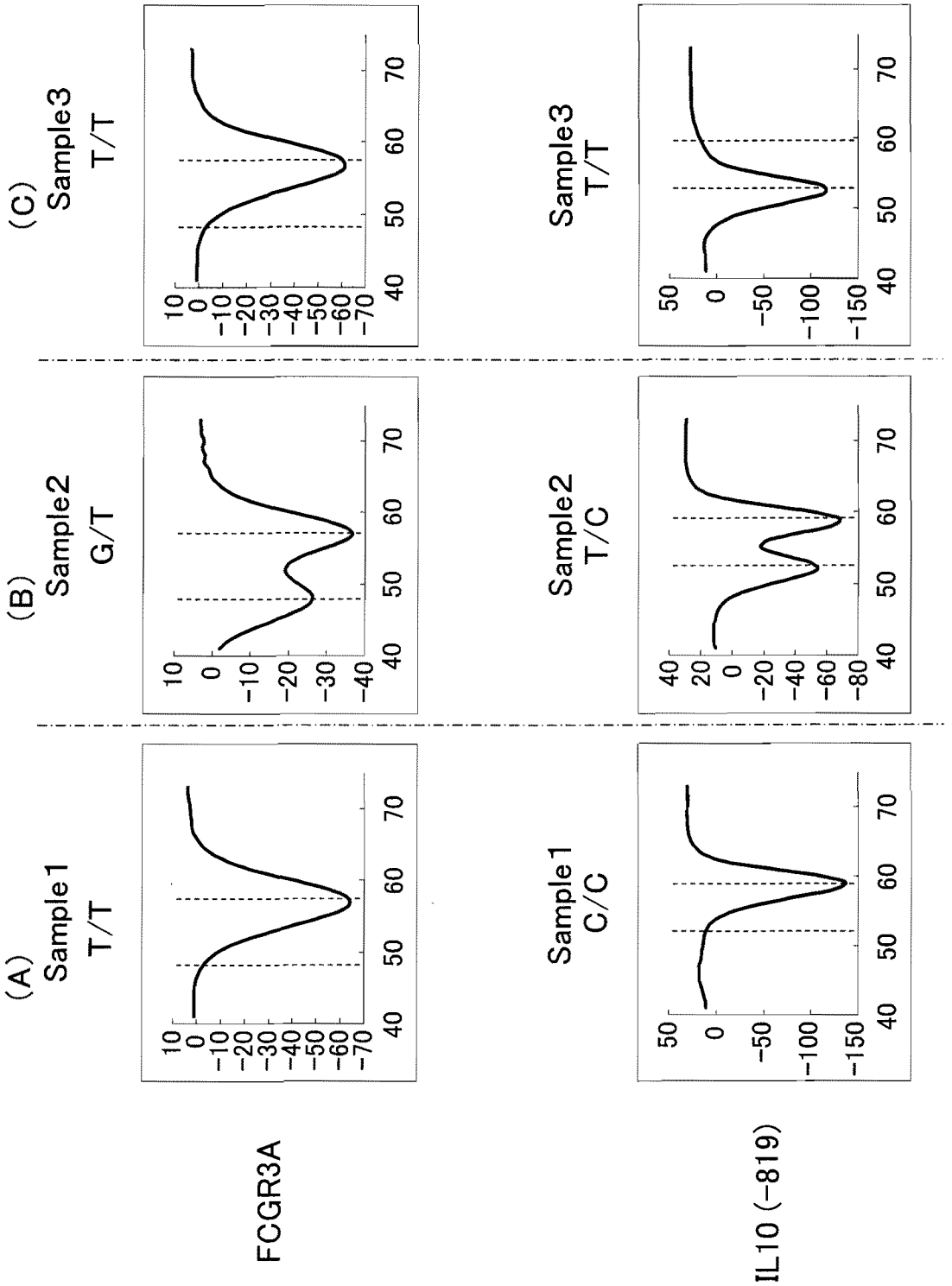
(A)
Sample1
T/T
(B)
Sample2
G/T
(C)
Sample3
T/T
FCGR3A
Sample1
C/C
Sample2
T/C
Sample3
T/T
IL10 (−819)

FIG. 1

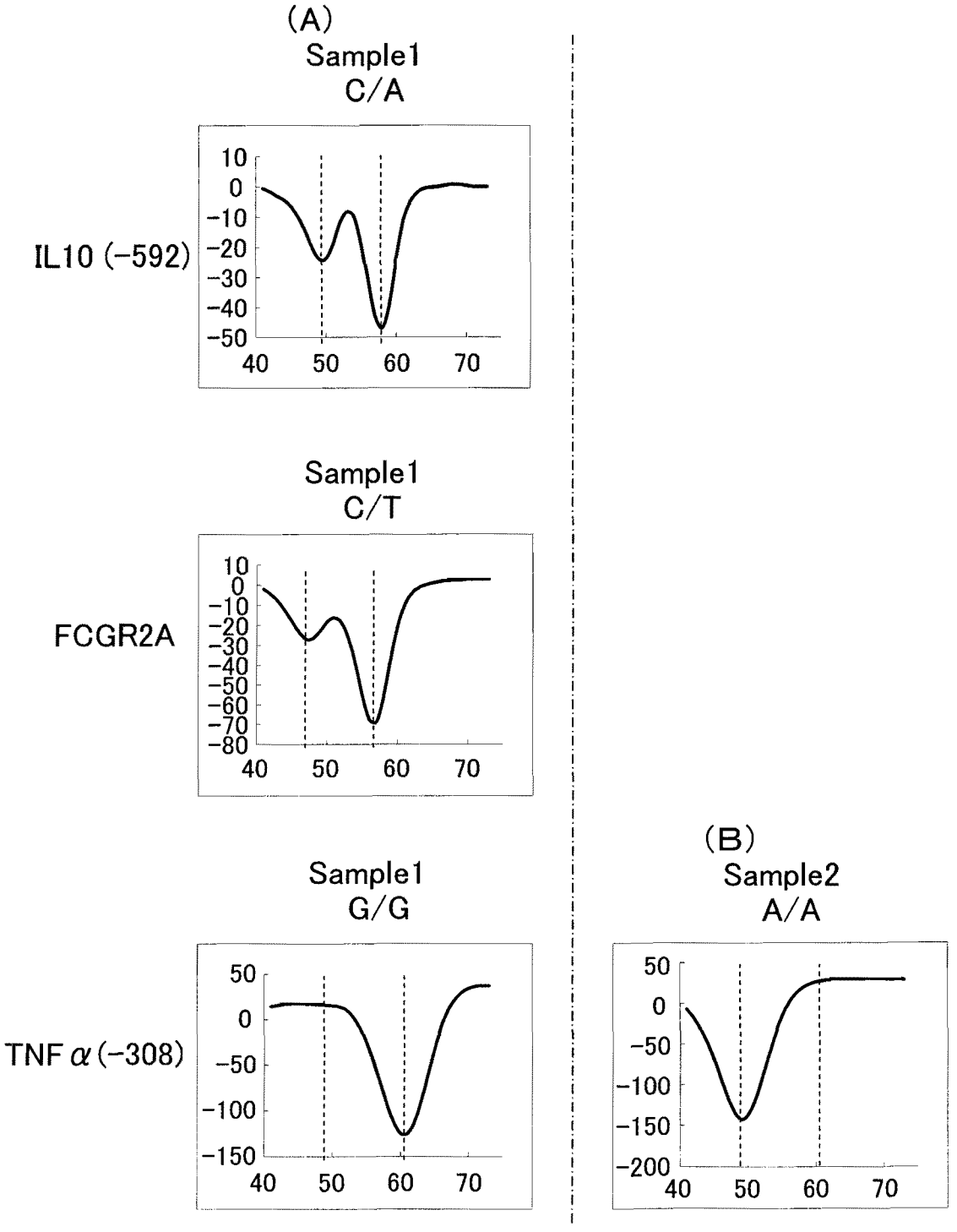
(A)
Sample1
C/A
IL10 (−592)
10
0
−10
−20
−30
−40
−50
40
50
60
70
Sample1
C/T
FCGR2A
10
0
−10
−20
−30
−40
−50
−60
−70
−80
40
50
60
70
Sample1
G/G
TNF α (−308)
50
0
−50
−100
−150
40
50
60
70
(B)
Sample2
A/A
50
0
−50
−100
−150
−200
40
50
60
70

FIG. 2

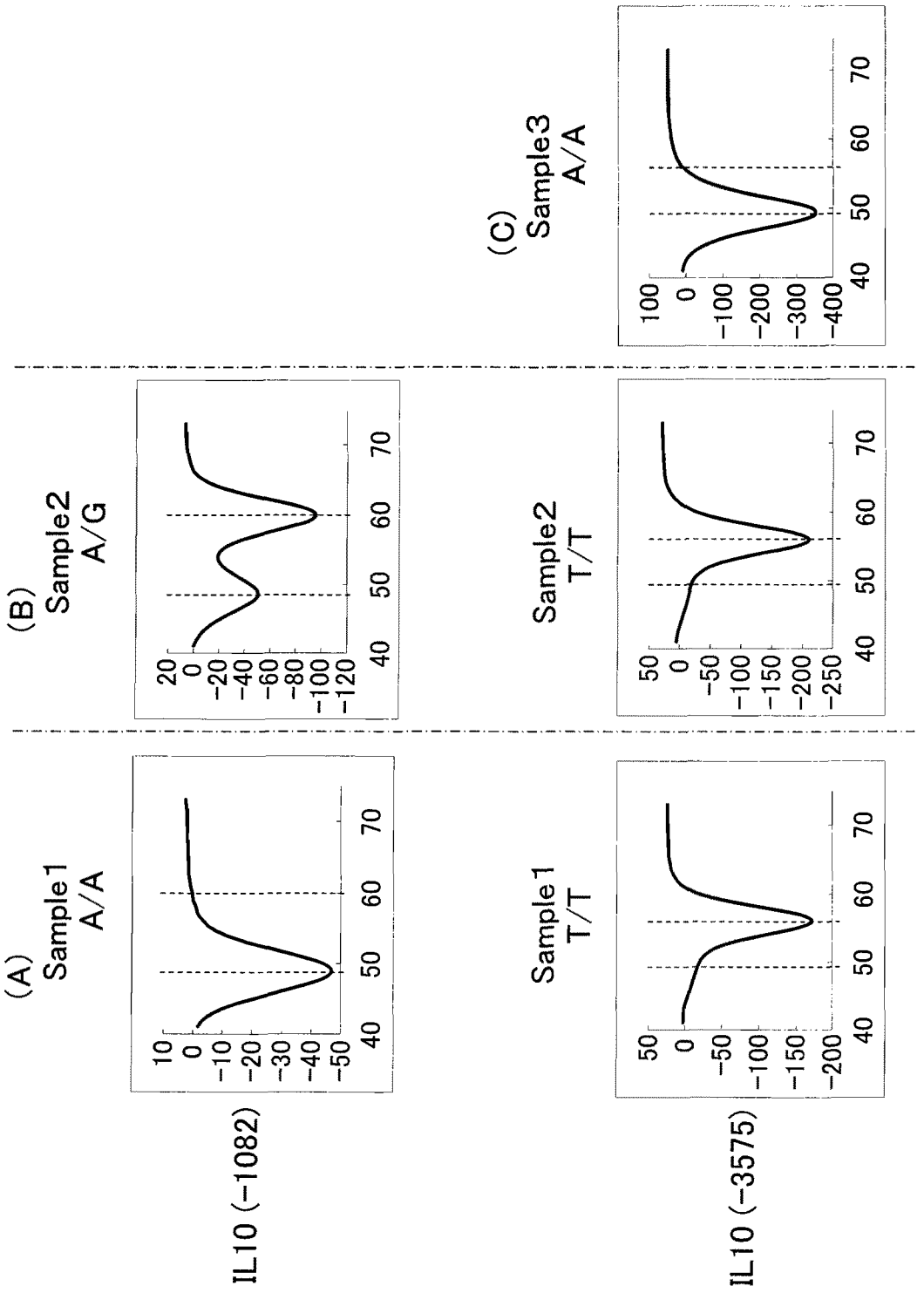
(A)
Sample1
A/A
(B)
Sample2
A/G
(C)
Sample3
A/A
Sample1
T/T
Sample2
T/T
IL10 (−1082)
IL10 (−3575)

FIG. 3

PROBES FOR DETECTING IMMUNE-RELATED GENE POLYMORPHISMS AND APPLICATIONS OF THE SAME

TECHNICAL FIELD

The present invention relates to probes for detecting polymorphisms of immune-related genes and to applications thereof.

BACKGROUND ART

Detection of a point mutation, a so-called single nucleotide polymorphism (SNP), is employed widely as a method of analyzing, at the gene level, for example, the causes of all types of diseases and the individual differences in disease liability (susceptibility to diseases) and in drug action.

Polymorphism detection methods that generally are practiced include (1) direct sequencing in which, in connection with the target DNA of a sample, a region to be detected is amplified by PCR (polymerase chain reaction) and the entire sequence of the amplification product thereof is analyzed; (2) PCR-RFLP (restriction fragment length polymorphism) in which PCR is performed in the same manner as in item (1) above, the amplification product is treated with restriction enzymes, and the change in restriction fragment length due to the polymorphisms is subjected to typing by Southern hybridization; and like methods.

However, the method of item (1) above requires, for example, sequencing after PCR and then electrophoresis or the like by a sequencer. The detection is thus very troublesome and costly. Moreover, the resulting amplification product needs to be subjected to treatment after PCR and may be contaminated during such treatment. The method of item (2) above also requires treatment of the resulting amplification product with a variety of restriction enzymes for analysis after PCR, thereby being troublesome. Moreover, the treatment of the resulting amplification product with restriction enzymes needs to be performed after the amplification product is transferred. Therefore, it may be possible that the amplification product obtained in a first reaction is scattered and may find another way into a second reaction that is performed separately. These problems cause another problem in that it is difficult with the methods of items (1) and (2) to automate the detection of point mutation.

Addressing these problems, a Tm (melting temperature) analysis recently has been attracting attention as a method for detecting an SNP. In this method, first, using a probe that is complementary to a region containing the SNP to be detected, a hybrid (double-strand nucleic acid) between a sample nucleic acid and the probe is formed. The hybridization product then is subjected to heat treatment, and the dissociation (melting) of the hybrid into a single-strand nucleic acid in response to a temperature increase is detected by measuring a signal such as absorbance. This is a method for determining an SNP by obtaining a Tm value based on the result of detection. The higher the homology of a hybridization product, the higher the Tm value, and the lower the homology, the lower the Tm value. Therefore, when the polymorphism of a detection target site is X or Y, a Tm value (reference value for evaluation) is obtained in advance in connection with a product of hybridization between a nucleic acid containing the desired polymorphism (for example, Y) and a probe that is 100% complementary thereto. Then, the Tm value of the sample nucleic acid and the probe is measured (measured value). When this measured value is identical to the reference value for evaluation, the sample nucleic acid and the probe perfectly match. That is, the detection target site of the sample nucleic acid can be determined as being of the desired polymorphism (Y). In contrast, when the measured value is lower than the reference value for evaluation, the sample nucleic acid and the probe mismatch. That is, the detection target site of the sample nucleic acid can be determined as having the other polymorphism (X). With such a method, an SNP can be detected, for example, only by subjecting a PCR reaction solution to which such a probe is added to thermal treatment and performing a signal measurement, and it is thus possible to automate a detection device.

However, such detection methods using Tm analysis have problems as follows. Generally, a gene polymorphism is present in the form of a homozygote (for example, X/X or Y/Y) or a heterozygote (for example, X/Y). It is important in the detection of a polymorphism to distinguish between a homozygote (X/X or Y/Y) and a heterozygote (X/Y) and, in the case of a homozygote, to distinguish between an X/X homozygote and a Y/Y homozygote. In the case of a heterozygote, gene polymorphism X and gene polymorphism Y are included, and the difference between these polymorphisms is merely a point mutation, i.e., a difference of one base. Accordingly, the following phenomenon occurs: a probe that fully hybridizes with a sequence that contains one polymorphism (for example, Y) (perfect-match) also hybridizes with a sequence that contains the other polymorphism (X) (single-base mismatch). In a case like this, there is a problem in that, as shown when a melting curve that indicates a relationship between signal intensity and temperature is drawn up based on a Tm analysis, it is difficult to detect a peak on the low-temperature side that indicates a mismatch sequence due to the presence of a peak on the high-temperature side that indicates a perfect-match sequence. That is, even when there is a mismatch sequence in a sample, the presence of a perfect-match sequence makes it difficult to distinguish the mismatch sequence, and thus it may be possible that the detection sensitivity is impaired. Also with respect to homozygotes, the difference between a homozygote (X/X) of a polymorphism X and a homozygote (Y/Y) of a polymorphism Y is likewise due to one base. Therefore, as described above, when it is difficult to distinguish between the peak of a perfect-match and the peak of a mismatch, it is consequently difficult to distinguish between a peak indicating the former (X/X) and a peak indicating the latter (Y/Y). That is, it may be possible to determine whether a sample is a homozygote, but it is likely to be difficult to determine the type of polymorphism.

Recently, antibody drugs that take advantage of the human immune function have been attracting attention in the field of pharmaceuticals. Examples of such antibody drugs include trade-name rituxan (generic name: rituximab), which is a therapeutic agent for malignant lymphoma, trade-name herceptin (generic name: trastuzumab), which is a therapeutic agent for breast cancer, and like agents. However, the strength of human immunity varies from person to person, and this is considered to have an influence on the pharmaceutical effects of such antibody drugs. Gene mutation (for example, SNP) is reported as a factor that has an influence on the pharmaceutical effect of such drugs. In particular, a polymorphism of the FCGR3A gene (Non-Patent Document 1), which is a gene that is involved in immunity, has been reported. This gene codes for FcγRIIIa, a type of fragment C receptor (FcR) of IgG. Hence, when such an antibody drug is used in medical treatment, it is considered useful, for example, to detect polymorphisms (SNPs) in such a gene and then to determine the course of medical treatment, e.g., the dosage of the antibody

drug and the change of a therapeutic agent, taking into consideration of the results of the detection.

Non-Patent Document 1: Buillaume Cartron et al., BLOOD, 1 Feb., 2002, Volume 99, Number 3

DISCLOSURE OF INVENTION

For the reasons described above, detection of a FCGR3A gene polymorphism is very important in, for example, medical treatment in which an antibody drug is used. The above-described problems are considered applicable not only to the FCGR3A gene but also to other immune-related genes, for example, the FCGR2A gene, the IL-10 gene, the TNF α gene and the TNF β gene. Hence, an object of the present invention is to provide, with respect to an immune-related gene, a polymorphism detection method that can distinguish in a simple manner and with excellent reliability a polymorphism that has one different base.

In order to achieve the object described above, a polymorphism detection probe of the present invention is composed of at least one oligonucleotide selected from the group consisting of oligonucleotides (A) to (H) below:

(A) at least one oligonucleotide complementary to a region extending from guanine at base 193 to be considered as the first base to any one of the 13^{rd} to 21^{st} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 1, with cytosine complementary to the guanine being the 3' end,

(B) at least one oligonucleotide complementary to a region extending from guanine at base 191 to be considered as the first base to any one of the 15^{th} to 24^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 2, with cytosine complementary to the guanine being the 3' end,

(C) at least one oligonucleotide complementary to a region extending from guanine at base 311 to be considered as the first base to any one of the 16^{th} to 21^{st} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 3, with cytosine complementary to the guanine being the 5' end,

(D) at least one oligonucleotide complementary to a region extending from guanine at base 391 to be considered as the first base to any one of the 16^{th} to 22^{nd} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 4, with cytosine complementary to the guanine being the 3' end,

(E) at least one oligonucleotide complementary to a region extending from guanine at base 426 to be considered as the first base to any one of the 15^{th} to 24^{th} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 5, with cytosine complementary to the guanine being the 5' end,

(F) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine at base 165 to be considered as the first base to any one of the 16^{th} to 27^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 6, with the cytosine being the 3' end,

(G) at least one oligonucleotide complementary to a region extending from guanine at base 394 to be considered as the first base to any one of the 12^{nd} to 16^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 7, with cytosine complementary to the guanine being the 3' end, and

(H) at least one oligonucleotide complementary to a region extending from guanine at base 393 to be considered as the first base to any one of the 15^{th} to 22^{nd} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 300, with cytosine complementary to the guanine being the 3' end.

The polymorphism detection reagent of the present invention is a reagent for detecting an immune-related gene polymorphism and contains a polymorphism detection probe of the present invention.

The polymorphism detection method of the present invention is a method for detecting an immune-related gene polymorphism and includes steps (1) to (3) as follows:

(1) a step of preparing a reaction system containing a sample nucleic acid for detecting the polymorphism and a polymorphism detection probe of the present invention;

(2) a step of measuring a signal value that indicates the melting state of the hybridization product between the sample nucleic acid and the probe while changing the temperature of the reaction system; and

(3) a step of determining the polymorphism in the sample nucleic acid based on the change in signal value associated with the temperature change.

With the probes of the present invention, specific polymorphisms as described below in connection with the immune-related genes, i.e., the FCGR3A gene, the FCGR2A gene, the IL-10 gene, the TNF α gene and the TNF β gene, can be distinguished in a simple manner and with excellent reliably by Tm analysis. In particular, even when an immune-related gene polymorphism is a heterozygote (X/Y), polymorphism X and polymorphism Y can be distinguished and detected. Moreover, when an immune-related gene polymorphism is a homozygote (X/X or Y/Y), it is also possible to distinguish between homozygote X/X and homozygote Y/Y. As described above, in the detection of a heterozygote (X/Y) by Tm analysis, conventional probes hybridize with a sequence containing one polymorphism (X) as well as a sequence containing the other polymorphism (Y) that is different only in one base, and therefore the signal peaks of both polymorphisms overlap in a melting curve, thereby making it difficult to distinguish between the polymorphisms. In contrast, with the probes of the present invention, signal peaks of both polymorphisms can be sufficiently distant from each other in a melting curve although the probes hybridize with both sequences. Therefore, according to the present invention, a polymorphism that has only one different base can be distinguished and detected in a simple manner. Moreover, according to the present invention, for example, even when two or more types of probes are introduced into a single reaction system, each probe can distinguish a corresponding immune-related gene polymorphism in the single reaction system. Therefore, a plurality of polymorphisms can be detected, for example, using a single reaction system for one sample. Accordingly, since an immune-related gene polymorphism readily can be distinguished with excellent reliability according to the present invention, the results of detection can be reflected also in, for example, a medical treatment with the administration of antibody drugs such as those described above. Therefore, it can be said that the present invention is particularly useful in the medical field and like technical fields.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** depicts graphs showing the results of a Tm analysis in Example 1 of the present invention.

FIG. **2** depicts graphs showing the results of a Tm analysis in Example 2 of the present invention.

FIG. **3** depicts graphs showing the results of a Tm analysis in Example 3 of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present specification, a site where a polymorphism to be detected occurs will be called hereinbelow a "detection target site", and a sequence with which a probe can hybridize

and that contains such a detection target site will be called a "detection target sequence". Encompassed within such detection target sequences, a detection target sequence that perfectly matches a probe will be called a "perfect-match sequence", and a detection target sequence that mismatches a probe will be called a "mismatch sequence". In the present specification, the term "perfect-match" means that the base of a detection target site is complementary to the corresponding base in a probe, and preferably means that the detection target sequence and the probe are fully complementary to each other. In the present invention, the term "mismatch" means that the base of a detection target site is non-complementary to the corresponding base in a probe, and preferably means that the detection target site and the probe are fully complementary in the sites other than the detection target site. In addition, a nucleic acid, DNA and a gene that have a perfect-match sequence will be called "a "perfect-match nucleic acid", "perfect-match DNA" and "a perfect-match gene", respectively, and a nucleic acid, DNA and a gene that have a mismatch sequence will be called "a mismatch nucleic acid", "mismatch DNA" and "a mismatch gene", respectively. Moreover, a nucleic acid, DNA and a gene on which polymorphism detection is performed will be called "a sample nucleic acid", "sample DNA" and "a sample gene", respectively.

Probes

The polymorphism detection probes of the present invention are, as described above, probes for detecting immune-related gene polymorphisms, and are composed of at least one oligonucleotide selected from the group consisting of items (A) to (H) as follows. The polymorphism detection probes of the present invention may contain, in addition to the following various oligonucleotides, for example, labeling materials or the like as will be described below.

FCGR3A Probe

A probe composed of an oligonucleotide (A) below is a probe for detecting a polymorphism of the FCGR3A gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "FCGR3A probe."

(A) at least one oligonucleotide complementary to a region extending from guanine (g) at base 193 to be considered as the first base to any one of the 13rd to 21st bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 1, with cytosine (c) complementary to the guanine being the 3' end.

The FCGR3A probe of the present invention is a probe for detecting a polymorphism (g/t, ancestral allele "g") of the 201st base (k) in the partial sequence of the FCGR3A gene shown in SEQ ID NO. 1. This polymorphism is registered under, for example, the NCBI accession NO. rs396991. In the present invention, this polymorphism will be called hereinbelow an "FCGR3A polymorphism."

The FCGR3A probe of the present invention is complementary to the sense strand (forward strand) of the FCGR3A gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (A), a complementary base that corresponds to the 201st base (k) of SEQ ID NO. 1 is represented as m, and this m is adenine or cytosine. When m is adenine, the probe perfectly matches a polymorphism (t), and when m is cytosine, the probe perfectly matches a polymorphism (g). Therefore, an FCGR3A polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, m is adenine.

Specific examples of the FCGR3A probe are presented in the following table. The probes represented by SEQ ID NOS. 8 to 16 have sequences complementary to regions that include the 201.sup.st base (k) in SEQ ID NO. 1, and the base m is a complementary base that corresponds to the 201.sup.st base (k) in SEQ ID NO. 1. In each of the sequences shown below, the base m may be either adenine (a) or cytosine (c), and it is preferably adenine (a). "Tm (° C.)" in the following table is the Tm (° C.) at which a sequence of the following table is hybridized with a fully complementary sequence, and the value is calculated with parameters such as an oligonucleotide concentration of 0.2 .mu.M and a sodium equivalent (Na eq.) of 50 mM using MELTCALC software (meltcalc.com/) (this also applies hereinbelow). A Tm value, as mentioned above, can be calculated using, for example, the aforementioned MELTCALC software (meltcalc.com/) or the like, and it also can be determined by the nearest neighbor method. Among the probes below, an oligonucleotide (A1) having the base sequence of SEQ ID NO. 14 is preferable.

TABLE 1

Probe	Sequence	Tm(° C.)	SEQ ID NO.
FCGR3A probes m = a, c	ttttactcccaamaagccccc-(fluorescent material)	54.6	8
	tttactcccaamaagccccc-(fluorescent material)	54	9
	ttactcccaamaagccccc-(fluorescent material)	53.4	10
	tactcccaamaagccccc-(fluorescent material)	52.7	11
	actcccaamaagccccc-(fluorescent material)	52.9	12
	ctcccaamaagccccc-(fluorescent material)	50.8	13
	tcccaamaagccccc-(fluorescent material)	49.1	14
	cccaamaagccccc-(fluorescent material)	46.9	15
	ccaamaagccccc-(fluorescent material)	42.8	16

Moreover, the FCGR3A probe of the present invention may be a probe composed of an oligonucleotide (A') that is complementary to the oligonucleotide (A). Thereby, hybridization with the antisense strand (reverse strand) allows the detection of a polymorphism in the antisense strand.

FCGR2A Probes

A probe composed of an oligonucleotide (B) below is a probe for detecting a polymorphism of the FCGR2A gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "FCGR2A probe."

(B) at least one oligonucleotide complementary to a region extending from guanine (g) at base 191 to be considered as the first base to any one of the 15th to 24th bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 2, with cytosine (c) complementary to the guanine being the 3' end.

The FCGR2A probe of the present invention is a probe for detecting a polymorphism (t/c, ancestral allele "t") of the 201st base (y) in the partial sequence of the FCGR2A gene shown in SEQ ID NO. 2. This polymorphism is registered under, for example, the NCBI accession NO. rs1801274. This polymorphism will be called hereinbelow an "FCGR2A polymorphism."

The FCGR2A probe of the present invention is complementary to the sense strand (forward strand) of the FCGR2A

gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (B), a complementary base that corresponds to the 201st base (y) of SEQ ID NO. 2 is represented as r, and this r is adenine or guanine. When r is guanine, the probe perfectly matches a polymorphism (c), and when r is adenine, the probe perfectly matches a polymorphism (t). Therefore, an FCGR2A polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, r is adenine.

Specific examples of the FCGR2A probe are presented in the following table. The probes represented by SEQ ID NOS. 17 to 26 have sequences complementary to regions that include the 201st base (y) in SEQ ID NO. 2, and the base r is a complementary base that corresponds to the 201st base (y) in SEQ ID NO. 2. In each of the sequences shown below, the base r may be either adenine (a) or guanine (g), and it is preferably adenine (a). Among the probes below, an oligonucleotide (B1) having the base sequence of SEQ ID NO. 23 is preferable.

TABLE 2

Probe	Sequence	Tm(° C.)	SEQ ID NO.
FCGR2A probes r = a, g	cagaaattctcccrtttggatccc-(fluorescent material)	55.3	17
	agaaattctcccrtttggatccc-(fluorescent material)	54.1	18
	gaaattctcccrtttggatccc-(fluorescent material)	52.9	19
	aaattctcccrtttggatccc-(fluorescent material)	51.8	20
	aattctcccrtttggatccc-(fluorescent material)	51	21
	attctcccrtttggatccc-(fluorescent material)	50.2	22
	ttctcccrtttggatccc-(fluorescent material)	49.7	23
	tctcccrtttggatccc-(fluorescent material)	48.7	24
	ctcccrtttggatccc-(fluorescent material)	46.8	25
	tcccrtttggatccc-(fluorescent material)	44.7	26

Moreover, the FCGR2A probe of the present invention may be a probe composed of an oligonucleotide (B') that is complementary to the oligonucleotide (B). Thereby, hybridization with the antisense strand (reverse strand) allows the detection of a polymorphism in the antisense strand.

example, the NCBI accession NO. rs1800872. This polymorphism will be called hereinbelow an "IL-10 (−592) polymorphism."

The IL-10 (−592) probe of the present invention is complementary to the sense strand of the IL-10 gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (C), a complementary base that corresponds to the 301st base (m) of SEQ ID NO. 3 is represented as k, and this k is thymine or guanine. When k is thymine, the probe perfectly matches a polymorphism (a), and when k is guanine, the probe perfectly matches a polymorphism (c). Therefore, an IL-10 (−592) polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, k is thymine.

Specific examples of the IL-10 (−592) probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 27 to 32 have sequences complementary to regions that include the 301st base (m) in SEQ ID NO. 3, and the base k is a complementary base that corresponds to the 301st base (m) in SEQ ID NO. 3. In each of the sequences shown below, the base k may be either thymine (t) or guanine (g), and it is preferably thymine (t). Among the probes below, an oligonucleotide (C1) having the base sequence of SEQ ID NO. 30 is preferable.

TABLE 3

Probe	Sequence	Tm(° C.)	SEQ ID NO.
IL10('1592) probes k = t, g	(fluorescent material)-cttcctacagkacaggcgggg-P	57.9	27
	(fluorescent material)-cttcctacagkacaggcggg-P	55.7	28
	(fluorescent material)-cttcctacagkacaggcgg-P	53.2	29
	(fluorescent material)-cttcctacagkacaggcg-P	50.6	30
	(fluorescent material)-cttcctacagkacaggc-P	47	31
	(fluorescent material)-cttcctacagkacagg-P	42.7	32

IL-10 (−592) Probes

A probe composed of an oligonucleotide (C) below is a probe for detecting the polymorphism at the 592nd site of the IL-10 gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "IL-10 (−592) probe."

(C) at least one oligonucleotide complementary to a region extending from guanine (G) at base 311 to be considered as the first base to any one of the 16th to 21st bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 3, with cytosine (C) complementary to the guanine being the 5' end.

The IL-10 (−592) probe of the present invention is a probe for detecting a polymorphism (a/c, ancestral allele "c") of the 301st base (m) in the partial sequence of the IL-10 gene shown in SEQ ID NO. 3. This polymorphism is registered under, for

Moreover, the IL-10 (−592) probe of the present invention may be a probe composed of an oligonucleotide (C') that is complementary to the oligonucleotide (C). Thereby, hybridization with the antisense strand allows detection of a polymorphism in the antisense strand.

IL-10 (−819) Probes

A probe composed of an oligonucleotide (D) below is a probe for detecting the polymorphism at the 819th site of the IL-10 gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "IL-10 (−819) probe." (D) at least one oligonucleotide complementary to a region extending from guanine (G) at base 391 to be considered as the first base to any one of the 16th to 22nd bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 4, with cytosine (C) complementary to the guanine being the 3' end.

The IL-10 (−819) probe of the present invention is a probe for detecting a polymorphism (c/t, ancestral allele "c") of the 401st base (y) in the partial sequence of the IL-10 gene shown in SEQ ID NO. 4. This polymorphism is registered under, for example, the NCBI accession NO. rs1800871. This polymorphism will be called hereinbelow an "IL-10 (−819) polymorphism."

The IL-10 (−819) probe of the present invention is complementary to the sense strand of the IL-10 gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (D), a complementary base that corresponds to the 401st base (y) of SEQ ID NO. 4 is represented as r, and this r is guanine or adenine. When r is guanine, the probe perfectly matches a polymorphism (c), and when r is adenine, the probe perfectly matches a polymorphism (t). Therefore, a polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, r is guanine.

Specific examples of the IL-10 (−819) probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 33 to 39 are composed of sequences complementary to regions that include the 401st base (y) in SEQ ID NO. 4, and the base r is a complementary base that corresponds to the 401st base (y) in SEQ ID NO. 4. In each of the sequences shown below, the base r may be either guanine (g) or adenine (a), and it is preferably guanine (g). Among the probes below, an oligonucleotide (D1) having the base sequence of SEQ ID NO. 36 is preferable.

TABLE 4

Probe	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-819) probes r = g, a	ggcacagagatrttacatcacc-(fluorescent material)	55	33
	gcacagagatrttacatcacc-(fluorescent material)	52.8	34
	cacagagatrttacatcacc-(fluorescent material)	49.6	35
	acagagatrttacatcacc-(fluorescent material)	47.9	36
	cagagatrttacatcacc-(fluorescent material)	45.8	37
	agagatrttacatcacc-(fluorescent material)	43.6	38
	gagatrttacatcacc-(fluorescent material)	41.5	39

Moreover, the IL-10 (−819) probe of the present invention may be a probe composed of an oligonucleotide (D') that is complementary to the oligonucleotide (D). Thereby, hybridization with the antisense strand allows the detection of a polymorphism in the antisense strand.

IL-10 (−1082) Probes

A probe composed of an oligonucleotide (E) below is a probe for detecting the polymorphism at the 1082nd site of the IL-10 gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "IL-10 (−1082) probe."

(E) at least one oligonucleotide complementary to a region extending from guanine (G) at base 426 to be considered as the first base to any one of the 15th to 24th bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 5, with cytosine (C) complementary to the guanine being the 5' end.

The IL-10 (−1082) probe of the present invention is a probe for detecting a polymorphism (a/g, ancestral allele "a") of the 414th base (r) in the partial sequence of the IL-10 gene shown in SEQ ID NO. 5. This polymorphism is registered under, for example, the NCBI accession NO. rs1800896. Hereinbelow, this polymorphism will be called an "IL-10 (−1082) polymorphism."

The IL-10 (−1082) probe of the present invention is complementary to the sense strand of the IL-10 gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (E), a base that is complementary to the 414th base (r) of SEQ ID NO. 5 is represented as y, and this y is thymine or cytosine. When y is thymine, the probe perfectly matches a polymorphism (a), and when y is cytosine, the probe perfectly matches a polymorphism (g). Therefore, a polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, y is cytosine.

Specific examples of the IL-10 (−1082) probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 40 to 49 have sequences complementary to regions that include the 414th base (r) in SEQ ID NO. 5, and the base y is a base complementary to the 414th base (r) in SEQ ID NO. 5. In each of the sequences shown below, the base y may be either thymine (t) or cytosine (c), and it is preferably cytosine (c). Among the probes below, an oligonucleotide (E1) having the base sequence of SEQ ID NO. 47 is preferable.

TABLE 5

Probe	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-1082) probes y = t, c	(fluorescent material)-ccctacttccccytcccaaagaag-P	59.5	40
	(fluorescent material)-ccctacttccccytcccaaagaa-P	58.9	41
	(fluorescent material)-ccctacttccccytcccaaaga-P	58.5	42
	(fluorescent material)-ccctacttccccytcccaaag-P	57.4	43
	(fluorescent material)-ccctacttccccytcccaaa-P	56.5	44
	(fluorescent material)-ccctacttccccytcccaa-P	56	45
	(fluorescent material)-ccctacttccccytccca-P	55.4	46
	(fluorescent material)-ccctacttccccytccc-P	53.5	47
	(fluorescent material)-ccctacttccccytcc-P	50.4	48
	(fluorescent material)-ccctacttccccytc-P	46.9	49

Moreover, the IL-10 (−1082) probe of the present invention may be a probe composed of an oligonucleotide (E') that is complementary to the oligonucleotide (E). Thereby, hybrid-

ization with the antisense strand allows detection of a polymorphism in the antisense strand.

IL-10(−3575) Probes

A probe composed of an oligonucleotide (F) below is a probe for detecting the polymorphism at the 3575th site of the IL-10 gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as an "IL-10 (−3575) probe."

(F) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (C) at base 165 to be considered as the first base to any one of the 16th to 27th bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 6, with the cytosine (C) being the 3' end.

The IL-10 (−3575) probe of the present invention is a probe for detecting a polymorphism (a/t, ancestral allele "t") of the 179th base (w) in the partial sequence of the IL-10 gene shown in SEQ ID NO. 6. This polymorphism is registered under, for example, the NCBI accession NO. rs1800890. This polymorphism will be called hereinbelow an "IL-10 (−3575) polymorphism."

The IL-10 (−3575) probe of the present invention is complementary to the antisense strand of the IL-10 gene, and hybridization with the antisense strand allows the detection of a polymorphism in the antisense strand. In the oligonucleotide (F), a base that corresponds to the 179th base (w) of SEQ ID NO. 6 is represented as w, and this w is thymine or adenine. When w is thymine, the probe perfectly matches a polymorphism (a) of the antisense strand, and when w is adenine, the probe perfectly matches a polymorphism (t) of the antisense strand. Therefore, a polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, w is thymine.

Specific examples of the IL-10 (−3575) probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 50 to 61 have sequences identical to regions that include the 179th base (w) in SEQ ID NO. 6, and the base w is a base that corresponds to the 179th base (w) in SEQ ID NO. 6. In the sequences shown below, the base w may be either thymine (t) or adenine (a), and it is preferably thymine (t). Among the probes below, an oligonucleotide (F1) having the base sequence of SEQ ID NO. 57 is preferable.

TABLE 6

Probe	Sequence	Tm(° C.)	SEQ ID NO.
IL10(−3575) probes w = t, a	(fluorescent material)-cccactggaaaaatwcatttaaaatca-P	53.2	50
	(fluorescent material)-cccactggaaaaatwcatttaaaatc-P	51.9	51
	(fluorescent material)-cccactggaaaaatwcatttaaaat-P	50.9	52
	(fluorescent material)-cccactggaaaaatwcatttaaaa-P	50.5	53
	(fluorescent material)-cccactggaaaaatwcatttaaa-P	49.8	54
	(fluorescent material)-cccactggaaaaatwcatttaa-P	49	55
	(fluorescent material)-cccactggaaaaatwcattta-P	48.2	56
	(fluorescent material)-cccactggaaaaatwcattt-P	48.2	57
	(fluorescent material)-cccactggaaaaatwcatt-P	47.3	58
	(fluorescent material)-cccactggaaaaatwcat-P	46.3	59
	(fluorescent material)-cccactggaaaaatwca-P	45.4	60
	(fluorescent material)-cccactggaaaaatwc-P	43	61

Moreover, the IL-10 (−3575) probe of the present invention may be a probe composed of an oligonucleotide (F') that is complementary to the oligonucleotide (F). Thereby, hybridization with the sense strand allows the detection of a polymorphism in the sense strand.

TNF α (−308) Probes

A probe composed of an oligonucleotide (G) below is a probe for detecting a polymorphism of the TNF α gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as a "TNF α (−308) probe" or a "TNF α probe."

(G) at least one oligonucleotide complementary to a region extending from guanine (G) at base 394 to be considered as the first base to any one of the 12nd to 16th bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 7, with cytosine (C) complementary to the guanine being the 3' end.

The TNF α probe of the present invention is a probe for detecting a polymorphism (a/g, ancestral allele "g") of the 401st base (r) in the partial sequence of the TNF α gene shown in SEQ ID NO. 7. This polymorphism is registered under, for example, the NCBI accession NO. rs1800629. Hereinbelow, this polymorphism will be called a "TNF α (−308) polymorphism" or "TNF α polymorphism."

The TNF α probe of the present invention is complementary to the sense strand of the TNF α gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (G), a base that is complementary to the 401st base (r) of SEQ ID NO. 7 is represented as y, and this y is thymine or cytosine. When y is thymine, the probe perfectly matches a polymorphism (a), and when y is cytosine, the probe perfectly matches a polymorphism (g). Therefore, a polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, y is cytosine.

Specific examples of the TNF α probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 62 to 66 have sequences complementary to regions that include the 401st base (r) in SEQ ID NO. 7, and the base y is a base complementary to the 401st base (r) in SEQ ID NO. 7. In the sequences shown below, the base y may be either thymine (t) or cytosine (c), and it is preferably cytosine (c). Among the probes below, an oligonucleotide (G1) composed of the base sequence of SEQ ID NO. 64 is preferable.

TABLE 7

Probe	Sequence	Tm(° C.)	SEQ ID NO.
TNF α (−308) probes	ccccgtccycatgccc-(fluorescent material)	58.6	62
	cccgtccycatgccc-(fluorescent material)	55.7	63

TABLE 7-continued

Probe	Sequence	Tm(° C.)	SEQ ID NO.
y = t, c	ccgtccycatgccc-(fluorescent material)	52.5	64
	cgtccycatgccc-(fluorescent material)	48.8	65
	gtccycatgccc-(fluorescent material)	43.6	66

Moreover, the TNF α probe of the present invention may be a probe composed of an oligonucleotide (G') that is complementary to the oligonucleotide (G). Thereby, hybridization with the antisense strand allows the detection of a polymorphism in the antisense strand.

TNF β Probes

A probe composed of an oligonucleotide (H) below is a probe for detecting a polymorphism of the TNF β gene, which is an immune-related gene. Hereinbelow, this probe will be referred to as a "TNF β (+252) probe" or a "TNF β probe."

(H) at least one oligonucleotide complementary to a region extending from guanine (G) at base 393 to be considered as the first base to any one of the 15^{th} to 22^{nd} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 300, with cytosine (C) complementary to the guanine being the 3' end.

The TNF β primer of the present invention is a probe for detecting a polymorphism (t/c) of the 401^{st} base (y) in the partial sequence of the TNF β gene shown in SEQ ID NO. 300. This polymorphism is registered under, for example, the NCBI accession NO. rs909253. Hereinbelow, this polymorphism will be called a "TNF β (+252) polymorphism" or a "TNF β polymorphism."

The TNF β probe of the present invention is complementary to the sense strand of the TNF β gene, and hybridization with the sense strand allows the detection of a polymorphism in the sense strand. In the oligonucleotide (H), a base that is complementary to the 401^{st} base (y) of SEQ ID NO. 300 is represented as r, and this r is adenine or guanine. When r is guanine, the probe perfectly matches a polymorphism (c), and when r is adenine, the probe perfectly matches a polymorphism (t). Therefore, a polymorphism can be detected based on whether the probe perfectly matches or not. Preferably, r is guanine.

Specific examples of the TNF β probe of the present invention are presented in the following table. The probes represented by SEQ ID NOS. 301 to 308 have sequences complementary to regions that include the 401^{th} base (y) in SEQ ID NO. 300, and the base r is a base complementary to the 401^{st} base (y) in SEQ ID NO. 300. In each of the sequences shown below, the base r may be either adenine (a) or guanine (g), and it is preferably guanine (g). Among the probes below, an oligonucleotide (H1) having the base sequence of SEQ ID NO. 306 or SEQ ID NO. 307 is preferable.

TABLE 8

Probe	Sequence	Tm(° C.)	SEQ ID NO.
TNF β (+252) probes r = a, g	tgtttctgccatgrttcctctc-(fluorescent material)	56.4	301
	gtttctgccatgrttcctctc-(fluorescent material)	54.9	302
	tttctgccatgrttcctctc-(fluorescent material)	53.6	303
	ttctgccatgrttcctctc-(fluorescent material)	52.9	304
	tctgccatgrttcctctc-(fluorescent material)	52.2	305
	ctgccatgrttcctctc-(fluorescent material)	50.6	306
	tgccatgrttcctctc-(fluorescent material)	48.9	307
	gccatgrttcctctc-(fluorescent material)	46.5	308

Moreover, the TNF β probe of the present invention may be a probe composed of an oligonucleotide (H') that is complementary to the oligonucleotide (H). Thereby, hybridization with the antisense strand allows the detection of a polymorphism in the antisense strand.

The probes of the present invention include probes that are composed of base sequences in which one or more bases are deleted, substituted or added at base sites other than the sites corresponding to the detection target sites in the oligonucleotides described above, and include probes that are composed of oligonucleotides that can hybridize with the detection target sequences.

The probes of the present invention preferably are labeled probes in which a labeling material is bonded to an aforementioned oligonucleotide. Examples of the labeled probes include a labeled probe that gives a signal when alone and that does not give any signal when forming a hybrid and a labeled probe that does not give any signal when alone and that gives a signal when forming a hybrid. The former probe does not give any signal when forming a hybrid (double-strand nucleic acid) with a detection target sequence, and gives a signal when the probe is liberated by heating. Moreover, the latter probe gives a signal when forming a hybrid (double-strand nucleic acid) with a detection target sequence, and the signal is diminished (quenched) when the probe is liberated by heating.

The labeling material is not limited and examples include fluorescent dyes (fluorophores). A probe that is labeled with a fluorescent dye, that emits fluorescence when alone and whose fluorescence is reduced (for example, quenched) when forming a hybrid is preferable as a specific example of the labeled probe. Probes that take advantage of such a fluorescence quenching phenomenon are called fluorescence quenching probes. It is preferable that in such a labeled probe the 3' end or the 5' end of an oligonucleotide is labeled with a fluorescent dye, and it is more preferable that, of the 3' end and the 5' end, the nucleotide end whose base is cytosine is labeled. In this case, it is preferable that, in connection with a detection target sequence with which the labeled probe hybridizes, the base sequence of the labeled probe is designed such that the base that forms a pair with the end-base cytosine of the labeled probe or the base that is located 1 to 3 bases distant from the base that forms a pair is guanine. Such probes generally are referred to as guanine-quenching probes and known as so-called QProbes (registered trademark). When such a guanine-quenching probe hybridizes with a detection target sequence, the guanine-quenching probe exhibits a phenomenon in which the end cytosine that is labeled with a

fluorescent dye nears the guanine present in the detection targeting sequence, and the fluorescence of the fluorescent dye thereby becomes weak (the intensity of fluorescence is reduced).

The fluorescent dyes are not limited and examples include fluoresceins, phosphors, rhodamine, polymethine dye derivatives, etc., and examples of commercially available fluorescent dyes include BODIPY FL (trade name, manufactured by Molecular Probes), FluorePrime (trade name, manufactured by Amersham Pharmacia), Fluoredite (trade name, manufactured by Millipore Corporation), FAM (manufactured by ABI), Cy3 and Cy5 (manufactured by Amersham Pharmacia), TAMRA (manufactured by Molecular Probes), Pacific Blue (manufactured by Becton, Dickinson and Company), etc. The conditions for detecting a probe are not particularly limited and can be determined suitably according to the fluorescent dye to be used. For example, Pacific Blue can be detected with a detection wavelength of 450 to 480 nm, TAMRA can be detected with a detection wavelength of 585 to 700 nm, and BODIPY FL can be detected with a detection wavelength of 515 to 555 nm. With the use of such a probe, hybridization and the dissociation thereof can be readily checked according to a change in signal.

Moreover, in the probes of the present invention, a phosphate group may be added to, for example, the 3' end. As described below, a sample nucleic acid can be prepared according to a nucleic acid amplification method such as PCR. In this instance, a probe of the present invention can be concomitantly present in the reaction system of the nucleic acid amplification reaction. In such a case, addition of a phosphate group to the 3' end of the probe sufficiently can prevent the elongation of the probe itself that could occur due to the nucleic acid amplification reaction. The same effect can be attained also by adding a labeling material as described above to the 3' end.

The probes of the present invention are each applicable to the detection of polymorphisms in various immune-related genes. In the detection of a polymorphism, one type of the probe of the present invention may be used to detect only one type of polymorphism, and two or more types of the probe may be used to detect two or more types of polymorphism. When two or more types of the probe of the present invention are used, for example, two or more types of polymorphism can be detected using a single reaction system in which the two or more types of the probe are concomitantly present. In this case, it is preferable to label each probe with a fluorescent dye that has a different detection condition.

In connection with the detection of polymorphisms using the probes of the present invention, detection methods are not at all limited insofar as they take advantage of the hybridization between the detection target sequences and the probes. A polymorphism detection method that uses a Tm analysis will be described below as an example of a method in which a probe of the present invention is applied.

Polymorphism Detection Method

The polymorphism detection method of the present invention is, as described above, a method for detecting an immune-related gene polymorphism and includes steps (1) to (3) as follows. The polymorphism detection method of the present invention uses a probe of the present invention, and any other configurations and conditions are not limited by the following description.

(1) A step of providing a reaction system containing a sample nucleic acid for detecting a polymorphism and a polymorphism detection probe of the present invention;

(2) A step of measuring a signal value that indicates the melting state of the hybridization product between the sample nucleic acid and the probe while changing the temperature of the reaction system; and

(3) A step of determining the polymorphism in the sample nucleic acid based on the change in signal value associated with the temperature change.

One or more types of the probe of the present invention may be used in the polymorphism detection method of the present invention as described above. In the former case, a polymorphism of one desired type can be detected in one reaction system and, in the latter case, the addition of two or more types of the probe of the present invention to a reaction system allows the detection of polymorphisms of two or more desired types that correspond to the respective probes in one reaction system. When two or more types of polymorphisms are to be detected in one reaction system, a combination of probes of the present invention is not particularly limited, and the following combinations can be mentioned as examples:

(1) A combination of the FCGR3A probe and the IL-10 (−819) probe, and preferably a combination of a probe containing the sequence of SEQ ID NO. 14 and a probe containing the sequence of SEQ ID NO. 36;

(2) A combination of the FCGR2A probe, the IL-10 (−592) probe and the TNF α (−308) probe, and preferably a combination of a probe containing the sequence of SEQ ID NO. 23, a probe containing the sequence of SEQ ID NO. 30 and a probe containing the sequence of SEQ ID NO. 64;

(3) A combination of the IL-10 (−1082) probe and the IL-10 (−3575) probe, and preferably a combination of a probe containing the sequence of SEQ ID NO. 47 and a primer containing the sequence of SEQ ID NO. 57; and

(4) A combination of the IL-10 (−592) probe and the IL-10 (−1082) probe, and preferably a combination of a probe containing the sequence of SEQ ID NO. 30 and a probe containing the sequence of SEQ ID NO. 47.

When two or more types of the probe are introduced into one reaction system, it is preferable that each probe is labeled with a labeling material that has a different detection condition. It is thus possible to detect two or more types of polymorphisms in a simple manner using a single reaction system merely by changing detection conditions.

In the present invention, the aforementioned sample nucleic acid may be a single-strand nucleic acid or double-strand nucleic acid. When the sample nucleic acid is a double-strand nucleic acid, it is preferable that the step (2) includes a step of dissociating the double-strand sample nucleic acid by heating the reaction system. The dissociation of the double-strand nucleic acid into a single strand nucleic acid allows hybridization with a probe of the present invention.

In the present invention, the nucleic acid may be, for example, a nucleic acid originally present in a biological sample, or may be an amplification product amplified according to a nucleic acid amplification method using the nucleic acid as a template nucleic acid because the accuracy of detection can be enhanced. The amplification product may be, for example, an amplification product produced using DNA present in a biological sample as a template, or an amplification product produced using cDNA as a template that is synthesized by RT-PCR from RNA such as total RNA or mRNA present in a biological sample.

When the sample nucleic acid is such an amplification product, a reaction system that contains a probe of the present invention and an amplification product may be provided in the step (1), for example, using an amplification product that is provided in advance, or a reaction system that contains a probe and an amplification product may be provided by

amplifying the desired amplification product from a template nucleic acid according to a nucleic acid amplification method in the presence of a probe of the present invention. In the latter case, it is preferable that the step (1) includes the step (1a) below:

(1a) a step of generating, in a reaction system containing a probe, an amplification product that serves as a sample nucleic acid from a template nucleic acid according to a nucleic acid amplification method.

The nucleic acid amplification method is not limited and examples include PCR (polymerase chain reaction), NASBA (nucleic acid sequence-based amplification), TMA (transcription-mediated amplification), SDA (strand displacement amplification), etc., with PCR being particularly preferable.

In the step (1a), it is preferable to use a primer for amplifying a sequence containing a polymorphism to be detected in an aforementioned immune-related gene. The sequence of the primer is not particularly limited and is sufficient insofar as it can amplify the detection target sequence containing the detection target site and it can be suitably arranged according to, for example, the detection target sequence and sequences in its vicinity using a known method. The length of the primer is not particularly limited, and can be set to a commonly used length such as, for example, 10 to 30 mer. When two or more types of polymorphisms are to be detected as described above, primers to amplify detection target sequences that are associated with respective polymorphisms may be used together. Moreover, the presence of such primers concomitantly in a single reaction system allows two or more types of detection target sequences to be amplified simultaneously.

For example, either a forward primer (hereinafter also referred to as an "F primer") that amplifies the sense strand of a gene or a reverse primer (hereinafter also referred to as an "R primer") that amplifies the antisense strand is usable as an aforementioned primer, and it is preferable to use a primer set containing both primers as a pair. Examples of such primer sets are given below. These are illustrative and do not limit the present invention.

FCGR3A Primer Set (a)

In connection with the detection of an FCGR3A polymorphism, an example of a primer set is a primer set (a) that contains a forward primer composed of an oligonucleotide (F1) below and a reverse primer composed of an oligonucleotide (R1) below.

(F1) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (c) at base 173 to be considered as the first base to any one of the 27^{th} to 46^{th} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 1, with the cytosine (c) being the 3' end, and

(R1) at least one oligonucleotide complementary to a region extending from adenine (a) at base 307 to be considered as the first base to any one of the 23^{rd} to 29^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 1, with thymine (t) complementary to the adenine (a) at base 307 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 77 and a reverse primer composed of the base sequence of SEQ ID NO. 97 is particularly preferable.

TABLE 9

Primer	Sequence	Tm(° C.)	SEQ ID NO.
FCGR3A F primers	tcatcataattctgacttctacattccaaaagccacactcaaagac	64.3	67
	catcataattctgacttctacattccaaaagccacactcaaagac	63.9	68
	atcataattctgacttctacattccaaaagccacactcaaagac	63.5	69
	tcataattctgacttctacattccaaaagccacactcaaagac	63.6	70
	cataattctgacttctacattccaaaagccacactcaaagac	63.1	71
	ataattctgacttctacattccaaaagccacactcaaagac	62.7	72
	taattctgacttctacattccaaaagccacactcaaagac	62.7	73
	aattctgacttctacattccaaaagccacactcaaagac	63	74
	attctgacttctacattccaaaagccacactcaaagac	63	75
	ttctgacttctacattccaaaagccacactcaaagac	63	76
	tctgacttctacattccaaaagccacactcaaagac	62.9	77
	ctgacttctacattccaaaagccacactcaaagac	62.3	78
	tgacttctacattccaaaagccacactcaaagac	62	79
	gacttctacattccaaaagccacactcaaagac	61.2	80
	acttctacattccaaaagccacactcaaagac	60.8	81
	cttctacattccaaaagccacactcaaagac	59.9	82
	ttctacattccaaaagccacactcaaagac	59.4	83
	tctacattccaaaagccacactcaaagac	59.2	84
	ctacattccaaaagccacactcaaagac	58.3	85
	tacattccaaaagccacactcaaagac	57.7	86
FCGR3A R primers	aatcaggaatctcctcccaactcaacttcccagtgtgat	66.3	87
	atcaggaatctcctcccaactcaacttcccagtgtgat	66.4	88
	tcaggaatctcctcccaactcaacttcccagtgtgat	66.5	89
	caggaatctcctcccaactcaacttcccagtgtgat	66	90
	aggaatctcctcccaactcaacttcccagtgtgat	65.6	91
	ggaatctcctcccaactcaacttcccagtgtgat	65	92
	gaatctcctcccaactcaacttcccagtgtgat	63.8	93
	aatctcctcccaactcaacttcccagtgtgat	63.5	94
	atctcctcccaactcaacttcccagtgtgat	63.4	95
	tctcctcccaactcaacttcccagtgtgat	63.5	96
	ctcctcccaactcaacttcccagtgtgat	62.8	97
	tcctcccaactcaacttcccagtgtgat	62.4	98
	cctcccaactcaacttcccagtgtgat	61.6	99
	ctcccaactcaacttcccagtgtgat	60	100
	tcccaactcaacttcccagtgtgat	59.4	101
	cccaactcaacttcccagtgtgat	58.4	102
	ccaactcaacttcccagtgtgat	56.5	103

FCGR2A Primer Set (b)

In connection with the detection of an FCGR2A polymorphism, an example of a primer set is a primer set (b) that contains a forward primer composed of an oligonucleotide (F2) below and a reverse primer composed of an oligonucleotide (R2) below.

A primer set containing a forward primer composed of an oligonucleotide (F2) below and a reverse primer composed of an oligonucleotide (R2) below: (F2) at least one oligonucleotide having a sequence identical to that of a region extending from guanine (g) at base 189 to be considered as the first base to any one of the 23rd to 38th bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 2, with the guanine (g) being the 3' end, and (R2) at least one oligonucleotide complementary to a region extending from guanine (g) at base 206 to be considered as the first base to any one of the 31st to 48th bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 2, with cytosine (c) complementary to the guanine (g) at base 206 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing an F2 primer composed of the base sequence of SEQ ID NO. 132 and an R2 primer composed of the base sequence of SEQ ID NO. 114 is particularly preferable.

IL-10 (−592) Primer Set (c)

In connection with the detection of an IL-10 (−592) polymorphism, an example of a primer set is a primer set (c) that contains a forward primer composed of an oligonucleotide (F3) below and a reverse primer composed of an oligonucleotide (R3) below.

(F3) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (c) at base 291 to be considered as the first base to any one of the 23rd to 41st bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 3, with the cytosine (c) being the 3' end, and

(R3) at least one oligonucleotide complementary to a region extending from guanine (g) at base 311 to be considered as the first base to any one of the 27th to 41st bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 3, with cytosine (c) complementary to the guanine (g) at base 311 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 148 and a reverse primer composed of the base sequence of SEQ ID NO. 167 is particularly preferable.

TABLE 10

Primer	Sequence	Tm(° C.)	SEQ ID NO.
FCGR2A F primers	accactgtgactgtggtttgcttgtgggatggagaagg	68.9	122
	ccactgtgactgtggtttgcttgtgggatggagaagg	68.3	123
	cactgtgactgtggtttgcttgtgggatggagaagg	67.3	124
	actgtgactgtggtttgcttgtgggatggagaagg	67	125
	ctgtgactgtggtttgcttgtgggatggagaagg	66.3	126
	tgtgactgtggtttgcttgtgggatggagaagg	66.1	127
	gtgactgtggtttgcttgtgggatggagaagg	65.4	128
	tgactgtggtttgcttgtgggatggagaagg	65	129
	gactgtggtttgcttgtgggatggagaagg	64.1	130
	actgtggtttgcttgtgggatggagaagg	63.8	131
	ctgtggtttgcttgtgggatggagaagg	62.9	132
	tgtggtttgcttgtgggatggagaagg	62.5	133
	gtggtttgcttgtgggatggagaagg	61.5	134
	tggtttgcttgtgggatggagaagg	60.7	135
	ggtttgcttgtgggatggagaagg	59.6	136
	gtttgcttgtgggatggagaagg	57.7	137
FCGR2A R primers	cctctggtcaaggtcacattcttccagaatggaaaatcccagaaattc	67.2	104
	ctctggtcaaggtcacattcttccagaatggaaaatcccagaaattc	66.5	105
	tctggtcaaggtcacattcttccagaatggaaaatcccagaaattc	66.3	106
	ctggtcaaggtcacattcttccagaatggaaaatcccagaaattc	65.9	107
	tggtcaaggtcacattcttccagaatggaaaatcccagaaattc	65.7	108
	ggtcaaggtcacattcttccagaatggaaaatcccagaaattc	65.2	109
	gtcaaggtcacattcttccagaatggaaaatcccagaaattc	64.3	110
	tcaaggtcacattcttccagaatggaaaatcccagaaattc	63.9	111
	caaggtcacattcttccagaatggaaaatcccagaaattc	63.4	112
	aaggtcacattcttccagaatggaaaatcccagaaattc	63	113
	aggtcacattcttccagaatggaaaatcccagaaattc	62.9	114
	ggtcacattcttccagaatggaaaatcccagaaattc	62.3	115
	gtcacattcttccagaatggaaaatcccagaaattc	61.2	116
	tcacattcttccagaatggaaaatcccagaaattc	60.6	117
	cacattcttccagaatggaaaatcccagaaattc	60	118
	acattcttccagaatggaaaatcccagaaattc	59.4	119
	cattcttccagaatggaaaatcccagaaattc	58.4	120
	attcttccagaatggaaaatcccagaaattc	57.7	121

TABLE 11

Primer	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-592) F primers	atgaaatcggggtaaaggagcctggaacacatcctgtgac	68.2	138
	tgaaatcggggtaaaggagcctggaacacatcctgtgac	68.3	139
	gaaatcggggtaaaggagcctggaacacatcctgtgac	67.7	140
	aaatcggggtaaaggagcctggaacacatcctgtgac	67.6	141
	aatcggggtaaaggagcctggaacacatcctgtgac	67.7	142
	atcggggtaaaggagcctggaacacatcctgtgac	67.7	143
	tcggggtaaaggagcctggaacacatcctgtgac	67.9	144
	cggggtaaaggagcctggaacacatcctgtgac	67.4	145
	ggggtaaaggagcctggaacacatcctgtgac	66.1	146
	gggtaaaggagcctggaacacatcctgtgac	64.9	147
	ggtaaaggagcctggaacacatcctgtgac	63.6	148
	gtaaaggagcctggaacacatcctgtgac	62.2	149
	taaaggagcctggaacacatcctgtgac	61.6	150
	aaaggagcctggaacacatcctgtgac	62.1	151
	aaggagcctggaacacatcctgtgac	61.9	152
	aggagcctggaacacatcctgtgac	61.8	153
	aggagcctggaacacatcctgtgac	60.9	154
	ggagcctggaacacatcctgtgac	59	155
	gagcctggaacacatcctgtgac	58.3	156
IL10(-592) R primers	gttcccaagcagcccttccatttactttccagagactggc	68.8	157
	ttcccaagcagcccttccatttactttccagagactggc	68.6	158
	tcccaagcagcccttccatttactttccagagactggc	68.7	159
	cccaagcagcccttccatttactttccagagactggc	68.2	160
	ccaagcagcccttccatttactttccagagactggc	67.2	161
	caagcagcccttccatttactttccagagactggc	66.2	162
	aagcagcccttccatttactttccagagactggc	65.9	163
	agcagcccttccatttactttccagagactggc	65.9	164
	gcagcccttccatttactttccagagactggc	65.3	165
	cagcccttccatttactttccagagactggc	63.8	166
	agcccttccatttactttccagagactggc	63.3	167
	gcccttccatttactttccagagactggc	62.6	168
	ccttccatttactttccagagactggc	60.7	169
	cttccatttactttccagagactggc	59.2	170
	ttccatttactttccagagactggc	57.6	171

IL-10 (−819) Primer Set (d)

In connection with the detection of an IL-10 (−819) polymorphism, an example of a primer set is a primer set (d) that contains a forward primer composed of an oligonucleotide (F4) below and a reverse primer composed of an oligonucleotide (R4) below.

(F4) at least one oligonucleotide having a sequence identical to that of a region extending from guanine (g) at base 351 to be considered as the first base to any one of the 24^{th} to 39^{th} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 4, with the guanine (g) being the 3' end, and

(R4) at least one oligonucleotide complementary to a region extending from guanine (g) at base 420 to be considered as the first base to any one of the 29^{th} to 46^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 4, with cytosine (c) complementary to the guanine (g) at base 420 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 182 and a reverse primer composed of the base sequence of SEQ ID NO. 198 is particularly preferable.

TABLE 12

Primer	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-819) F primers	tcattctatgtgctggagatggtgtacagtagggtgagg	66.1	172
	cattctatgtgctggagatggtgtacagtagggtgagg	65.6	173
	attctatgtgctggagatggtgtacagtagggtgagg	65.2	174
	ttctatgtgctggagatggtgtacagtagggtgagg	65.3	175
	tctatgtgctggagatggtgtacagtagggtgagg	65.3	176
	ctatgtgctggagatggtgtacagtagggtgagg	64.7	177
	tatgtgctggagatggtgtacagtagggtgagg	64.5	178
	atgtgctggagatggtgtacagtagggtgagg	65	179
	tgtgctggagatggtgtacagtagggtgagg	65.1	180
	gtgctggagatggtgtacagtagggtgagg	64.2	181
	tgctggagatggtgtacagtagggtgagg	63.7	182
	gctggagatggtgtacagtagggtgagg	62.8	183
	ctggagatggtgtacagtagggtgagg	60.8	184
	tggagatggtgtacagtagggtgagg	60.3	185
	ggagatggtgtacagtagggtgagg	59.5	186
	gagatggtgtacagtagggtgagg	57.4	187

TABLE 12-continued

Primer	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-819) R primers	aggtagtgctcaccatgacccctaccgtctctattttatagtgagc	67.9	188
	ggtagtgctcaccatgacccctaccgtctctattttatagtgagc	67.5	189
	gtagtgctcaccatgacccctaccgtctctattttatagtgagc	66.7	190
	tagtgctcaccatgacccctaccgtctctattttatagtgagc	66.5	191
	agtgctcaccatgacccctaccgtctctattttatagtgagc	66.9	192
	gtgctcaccatgacccctaccgtctctattttatagtgagc	66.4	193
	tgctcaccatgacccctaccgtctctattttatagtgagc	66.1	194
	gctcaccatgacccctaccgtctctattttatagtgagc	65.5	195
	ctcaccatgacccctaccgtctctattttatagtgagc	64.2	196
	tcaccatgacccctaccgtctctattttatagtgagc	63.9	197
	caccatgacccctaccgtctctattttatagtgagc	63.4	198
	accatgacccctaccgtctctattttatagtgagc	62.9	199
	ccatgacccctaccgtctctattttatagtgagc	62.1	200
	catgacccctaccgtctctattttatagtgagc	60.9	201
	atgacccctaccgtctctattttatagtgagc	60.3	202
	tgacccctaccgtctctattttatagtgagc	60.2	203
	gacccctaccgtctctattttatagtgagc	59.3	204
	accctaccgtctctattttatagtgagc	58.8	205

IL-10 (−1082) Primer Set (e)

In connection with the detection of an IL-10 (−1082) polymorphism, an example of a primer set is a primer set (e) that contains a forward primer composed of an oligonucleotide (F5) below and a reverse primer composed of an oligonucleotide (R5) below.

(F5) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (c) at base 329 to be considered as the first base to any one of the 22^{nd} to 32^{nd} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 5, with the cytosine (c) being the 3' end, and

(R5) at least one oligonucleotide complementary to a region extending from guanine (g) at base 447 to be considered as the first base to any one of the 23^{rd} to 39^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 5, with cytosine (c) complementary to the guanine (g) at base 447 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 213 and a reverse primer composed of the base sequence of SEQ ID NO. 227 is particularly preferable.

TABLE 13

Probe	Sequence	Tm(° C.)	SEQ ID NO.
IL10(-1082) F primers	ctcctcgccgcaacccaactggctctccttac	69.2	206
	tcctcgccgcaacccaactggctctccttac	69.2	207
	cctcgccgcaacccaactggctctccttac	68.6	208
	ctcgccgcaacccaactggctctccttac	67.4	209
	tcgccgcaacccaactggctctccttac	67.2	210
	cgccgcaacccaactggctctccttac	66.6	211
	gccgcaacccaactggctctccttac	65	212
	ccgcaacccaactggctctccttac	63	213
	cgcaacccaactggctctccttac	61.4	214
	gcaacccaactggctctccttac	59.3	215
	caacccaactggctctccttac	56.7	216
IL10(-1082) R primers	aaagaagtcaggattccatggaggctggataggaggtcc	67.4	217
	aagaagtcaggattccatggaggctggataggaggtcc	67.5	218
	agaagtcaggattccatggaggctggataggaggtcc	67.5	219
	gaagtcaggattccatggaggctggataggaggtcc	67	220
	aagtcaggattccatggaggctggataggaggtcc	66.8	221
	agtcaggattccatggaggctggataggaggtcc	66.9	222
	gtcaggattccatggaggctggataggaggtcc	66.3	223
	tcaggattccatggaggctggataggaggtcc	65.9	224
	caggattccatggaggctggataggaggtcc	65.3	225
	aggattccatggaggctggataggaggtcc	64.8	226
	ggattccatggaggctggataggaggtcc	64.2	227
	gattccatggaggctggataggaggtcc	62.7	228
	attccatggaggctggataggaggtcc	62.3	229
	ttccatggaggctggataggaggtcc	62.3	230
	tccatggaggctggataggaggtcc	62.2	231
	ccatggaggctggataggaggtcc	61.3	232
	catggaggctggataggaggtcc	59.5	233

IL-10 (−3575) Primer Set (f)

In connection with the detection of an IL-10 (−3575) polymorphism, an example of a primer set is a primer set containing a forward primer composed of an oligonucleotide (F6) below and a reverse primer composed of an oligonucleotide (R6) below.

(F6) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (c) at base 139 to be considered as the first base to any one of the 25^{th} to 42^{nd} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 6, with the cytosine (c) being the 3' end, and

(R6) at least one oligonucleotide complementary to a region extending from guanine (g) at base 223 to be considered as the first base to any one of the 19^{th} to 33^{rd} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 6, with cytosine (c) complementary to the guanine (g) at base 223 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 244 and a reverse primer composed of the base sequence of SEQ ID NO. 260 is particularly preferable.

TNF α Primer Set (g)

In connection with the detection of a TNF α polymorphism, an example of a primer set is a primer set containing a forward primer composed of an oligonucleotide (F7) below and a reverse primer composed of an oligonucleotide (R7) below.

(F7) at least one oligonucleotide having a sequence identical to that of a region extending from guanine (g) at base 386 to be considered as the first base to any one of the 26^{th} to 41^{st} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 7, with the guanine (g) being the 3' end, and (R7) at least one oligonucleotide complementary to a region extending from cytosine (c) at base 418 to be considered as the first base to any one of the 24^{th} to 40^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 7, with guanine (g) complementary to the cytosine (c) at base 418 being the 3' end.

Specific examples of forward primers and reverse primers are given below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 277 and a reverse primer composed of the base sequence of SEQ ID NO. 293 is particularly preferable.

TABLE 14

Primer	Sequence	Tm(° C.)	SEQ ID NO.
IL10(−3575) F primers	agaggagcagggatggaagaagagaggtattccccttcccac	69.8	234
	gaggagcagggatggaagaagagaggtattccccttcccac	69.4	235
	aggagcagggatggaagaagagaggtattccccttcccac	69.3	236
	ggagcagggatggaagaagagaggtattccccttcccac	68.8	237
	gagcagggatggaagaagagaggtattccccttcccac	67.9	238
	agcagggatggaagaagagaggtattccccttcccac	67.8	239
	gcagggatggaagaagagaggtattccccttcccac	67.3	240
	cagggatggaagaagagaggtattccccttcccac	65.9	241
	agggatggaagaagagaggtattccccttcccac	65.5	242
	gggatggaagaagagaggtattccccttcccac	64.9	243
	ggatggaagaagagaggtattccccttcccac	63.7	244
	gatggaagaagagaggtattccccttcccac	62.4	245
	atggaagaagagaggtattccccttcccac	62	246
	tggaagaagagaggtattccccttcccac	62	247
	ggaagaagagaggtattccccttcecac	61	248
	gaagaagagaggtattccccttcccac	59.5	249
	aagaagagaggtattccccttcccac	58.9	250
	agaagagaggtattccccttcccac	58.6	251
IL10(−3573) R primers	gcctgagtccagtttgccctcaagcccagatgc	69.6	252
	cctgagtccagtttgccctcaagcccagatgc	68.2	253
	ctgagtccagtttgccctcaagcccagatgc	67	254
	tgagtccagtttgccctcaagcccagatgc	66.8	255
	gagtccagtttgccctcaagcccagatgc	66	256
	agtccagtttgccctcaagcccagatgc	65.8	257
	gtccagtttgccctcaagcccagatgc	65.1	258
	tccagtttgccctcaagcccagatgc	64.5	259
	ccagtttgccctcaagcccagatgc	63.8	260
	cagtttgccctcaagcccagatgc	62.1	261
	agtttgccctcaagcccagatgc	61.4	262
	gtttgccctcaagcccagatgc	60.4	263
	tttgccctcaagcccagatgc	59.5	264
	ttgccctcaagcccagatgc	59.2	265
	tgccctcaagcccagatgc	58.8	266

TABLE 15

Primer	Sequence	Tm(° C.)	SEQ ID NO.
TNFα(-308) F primers	agaccacagacctggtccccaaaagaaatggaggcaatagg	68.9	267
	gaccacagacctggtccccaaaagaaatggaggcaatagg	68.5	268
	accacagacctggtccccaaaagaaatggaggcaatagg	68.4	269
	ccacagacctggtccccaaaagaaatggaggcaatagg	67.8	270
	cacagacctggtccccaaaagaaatggaggcaatagg	66.8	271
	acagacctggtccccaaaagaaatggaggcaatagg	66.5	272
	cagacctggtccccaaaagaaatggaggcaatagg	65.8	273
	agacctggtccccaaaagaaatggaggcaatagg	65.4	274
	gacctggtccccaaaagaaatggaggcaatagg	64.8	275
	acctggtccccaaaagaaatggaggcaatagg	64.6	276
	cctggtccccaaaagaaatggaggcaatagg	63.7	277
	ctggtccccaaaagaaatggaggcaatagg	62.4	278
	tggtccccaaaagaaatggaggcaatagg	62	279
	ggtccccaaaagaaatggaggcaatagg	61	280
	gtccccaaaagaaatggaggcaatagg	59.5	281
	tccccaaaagaaatggaggcaatagg	58.6	282
TNFα(-308) R primers	gtcttctgggccactgactgatttgtgtgtaggaccctgg	69.3	283
	tcttctgggccactgactgatttgtgtgtaggaccctgg	69.1	284
	cttctgggccactgactgatttgtgtgtaggaccctgg	68.7	285
	ttctgggccactgactgatttgtgtgtaggaccctgg	68.6	286
	tctgggccactgactgatttgtgtgtaggaccctgg	68.7	287
	ctgggccactgactgatttgtgtgtaggaccctgg	68.2	288
	tgggccactgactgatttgtgtgtaggaccctgg	68	289
	gggccactgactgatttgtgtgtaggaccctgg	67.4	290
	ggccactgactgatttgtgtgtaggaccctgg	66.2	291
	gccactgactgatttgtgtgtaggaccctgg	65	292
	ccactgactgatttgtgtgtaggaccctgg	63.3	293
	cactgactgatttgtgtgtaggaccctgg	62	294
	actgactgatttgtgtgtaggaccctgg	61.3	295
	ctgactgatttgtgtgtaggaccctgg	60.3	296
	tgactgatttgtgtgtaggaccctgg	59.8	297
	gactgatttgtgtgtaggaccctgg	58.6	298
	actgatttgtgtgtaggaccctgg	57.9	299

TNF β Primer Set (h)

In connection with the detection of a TNF β polymorphism, an example of a primer set is a primer set containing a forward primer composed of an oligonucleotide (F8) below and a reverse primer composed of an oligonucleotide (R8) below.

(F8) at least one oligonucleotide having a sequence identical to that of a region extending from cytosine (c) at base 350 to be considered as the first base to any one of the 18^{th} to 37^{th} bases in the direction toward the 5' end in the base sequence of SEQ ID NO: 300, with the cytosine (c) being the 3' end, and (R8) at least one oligonucleotide complementary to a region extending from guanine (g) at base 443 to be considered as the first base to any one of the 17^{th} to 37^{th} bases in the direction toward the 3' end in the base sequence of SEQ ID NO: 300, with cytosine (c) complementary to the guanine (g) at base 443 being the 3' end.

Specific examples of forward primers and reverse primers are shown below, but the present invention is not limited by the examples. Moreover, combinations of the forward primers and the reverse primers are not at all limited and, among others, a primer set containing a forward primer composed of the base sequence of SEQ ID NO. 337 and a reverse primer composed of the base sequence of SEQ ID NO. 312 is particularly preferable.

TABLE 16

Primer	Sequence	Tm(° C.)	SEQ ID NO.
TNFB(+252) F primers	cgacagagaaggggacaagatgcagtcagagaaaccc	67.6	330
	gacagagaaggggacaagatgcagtcagagaaaccc	66.4	331
	acagagaaggggacaagatgcagtcagagaaaccc	66.3	332
	cagagaaggggacaagatgcagtcagagaaaccc	65.5	333
	agagaaggggacaagatgcagtcagagaaaccc	65.1	334
	gagaaggggacaagatgcagtcagagaaaccc	64.5	335
	agaaggggacaagatgcagtcagagaaaccc	64.2	336
	gaaggggacaagatgcagtcagagaaaccc	63.6	337
	aaggggacaagatgcagtcagagaaaccc	63.2	338
	aggggacaagatgcagtcagagaaaccc	63.1	339
	ggggacaagatgcagtcagagaaaccc	62.4	340
	gggacaagatgcagtcagagaaaccc	60.8	341
	ggacaagatgcagtcagagaaaccc	59.1	342
	gacaagatgcagtcagagaaaccc	57.3	343
	acaagatgcagtcagagaaaccc	56.6	344
	caagatgcagtcagagaaaccc	55.2	345
	aagatgcagtcagagaaaccc	53.9	346
	agatgcagtcagagaaaccc	53.3	347
	gatgcagtcagagaaaccc	51.9	348
	atgcagtcagagaaaccc	50.5	349

TABLE 16-continued

Primer	Sequence	Tm(° C.)	SEQ ID NO.
RNFB(+252)	tttggtttccttctctgtctctgactctccatctgtc	64.2	309
R primers	ttggtttccttctctgtctctgactctccatctgtc	64.2	310
	tggtttccttctctgtctctgactctccatctgtc	64.1	311
	ggtttccttctctgtctctgactctccatctgtc	63.4	312
	gtttccttctctgtctctgactctccatctgtc	62.2	313
	tttccttctctgtctctgactctccatctgtc	61.6	314
	ttccttctctgtctctgactctccatctgtc	61.5	315
	tccttctctgtctctgactctccatctgtc	61.3	316
	ccttctctgtctctgactctccatctgtc	60.6	317
	cttctctgtctctgactctccatctgtc	59.1	318
	ttctctgtctctgactctccatctgtc	58.5	319
	tctctgtctctgactctccatctgtc	58.2	320
	ctctgtctctgactctccatctgtc	57.3	321
	tctgtctctgactctccatctgtc	56.5	322
	ctgtctctgactctccatctgtc	55.4	323
	tgtctctgactctccatctgtc	54.5	324
	gtctctgactctccatctgtc	53	325
	tctctgactctccatctgtc	51.5	326
	ctctgactctccatctgtc	50	327
	tctgactctccatctgtc	48.5	328
	ctgactctccatctgtc	46.7	329

In the step (1), the proportion (molar ratio) of the probe of the present invention relative to the sample nucleic acid is not particularly limited, but since a detection signal can be obtained sufficiently, it is preferably equimolar or less, and more preferably 0.1 or less. Here, the sample nucleic acid may refer to, for example, the total of a perfect-match nucleic acid that has a perfect-match sequence and a mismatch nucleic acid that has a mismatch sequence or may refer to the total of an amplification product that contains a perfect-match sequence and an amplification product that contains a mismatch sequence. The proportion of perfect-match DNA in a sample nucleic acid is usually unknown, and it is preferable at the end that the proportion (molar ratio) of probe is 10 or less relative to a perfect-match nucleic acid (amplification product containing a perfect-match sequence), more preferably 5 or less, and even more preferably 3 or less. Moreover, the lower limit thereof is not particularly limited and, for example, it is 0.001 or greater, preferably 0.01 or greater, and more preferably 0.1 or greater. The proportion of the probe of the present invention relative to the sample nucleic acid may refer to, for example, a molar ratio relative to a double-strand nucleic acid or may refer to a molar ratio relative to a single strand nucleic acid.

Samples to which the polymorphism detection method of the present invention is applied are not particularly limited, and examples include biological samples. Specific examples of such biological samples include blood cells such as leukocyte cells, whole blood, buccal cells such as oral mucosa, somatic cells such as nail and hair, reproductive cells, sputa, amniotic fluids, paraffin-embedded tissues, urine, gastric fluids, gastric lavage fluids, etc. In the present invention, the method for collecting the sample, the method for preparing a sample nucleic acid from the sample and like methods are not limited, and a known method can be used.

A description is given of a Tm value here. As a solution containing a double-strand nucleic acid (for example, double-strand DNA) is heated, the absorbance at 260 nm is increased. This is because the hydrogen bonding between the strands in the double-strand nucleic acid is broken by heating, resulting in dissociation into a single-strand nucleic acid (for example, a single-strand DNA) (melting of DNA). When the entire double-strand nucleic acid is dissociated into a single-strand nucleic acid, the absorbance thereof is about 1.5 times greater than the absorbance at the beginning of heating (the absorbance of a double-strand nucleic acid only), and the completion of melting can be determined accordingly. Based on this phenomenon, a melting temperature Tm generally is defined as a temperature at which absorbance shows a 50% increase relative to the initial absorbance.

In the present invention, the measurement of a change in signal that is associated with a temperature change for determining a Tm value can be performed by measuring the absorbance at 260 nm according to the principle described above, and it is preferable to measure the signal of a labeling material added to a probe. Therefore, it is preferable to use the above-described labeled probes as the probes of the present invention. Examples of the labeled probes include a labeled probe that gives a signal when alone and that does not give any signal when forming a hybrid and a labeled probe that does not give any signal when alone and that gives a signal when forming a hybrid. The former probe does not give any signal when forming a hybrid (double-strand nucleic acid) with a detection target sequence and gives a signal when the probe is liberated by heating. Moreover, the latter probe gives a signal when forming a hybrid (double-strand nucleic acid) with a detection target sequence and the signal is reduced (quenched) when the probe is liberated by heating. Therefore, by detecting the signal of such a labeling material under conditions that are specific to the signal (absorbance and the like), the advancement of melting and a Tm value can be determined in the same manner as in the measurement of the absorption at 260 nm. Examples of labeling materials for use in labeled probes are as described above.

Next, the polymorphism detection method of the present invention will be described in reference to an example in which a nucleic acid amplification product is used as a sample nucleic acid and a labeled probe that is labeled with a fluorescent dye is used as a probe of the present invention. A feature of the polymorphism detection method of the present invention is the use of a probe of the present invention per se, and the method is not at all limited by other aspects such as processes or conditions.

First, genomic DNA is isolated from whole blood. Isolation of genomic DNA from whole blood can be performed according to a known method. For a specific example, a commercially available genomic DNA isolation kit (trade

name: GFX genomic blood DNA purification kit, manufactured by GE Healthcare Bioscience) or the like can be used.

Next, a labeled probe is added to a sample containing the isolated genomic DNA to prepare a reaction mixture. As described above, one type of labeled probe may be added, or two or more types of labeled probe may be added. For example, a QProbe is preferable as the labeled probe. A QProbe is generally a probe in which the cytosine at a probe end is labeled with a fluorescent dye, and due to the hybridization between this probe and a detection target sequence, the fluorescent dye and the guanine of the detection target sequence interact, resulting in a reduction in (or quenching of) fluorescence. The base sequence of the labeled probe is as described above, and it can be suitably selected according to the polymorphism to be detected.

The time to add the labeled probe is not particularly limited and, for example, addition to a PCR amplification product may be performed after a nucleic acid amplification reaction that will be described below, or addition may be performed before a nucleic acid amplification reaction. When the labeled probe is added before a nucleic acid amplification reaction such as PCR as described above, it is preferable, for example, to add a fluorescent dye or a phosphate group to the 3' end of the probe as described above.

The labeled probe may be added to a sample containing isolated genomic DNA or may be mixed with genomic DNA in a solvent. The solvent is not particularly limited and examples include buffers such as Tris-HCl; solvents containing KCl, $MgCl_2$, $MgSO_4$, glycerol and the like; reaction fluids for nucleic acid amplification such as reaction fluids for PCR; and those that are conventionally known.

Then, using the isolated genomic DNA as a template, a sequence that contains a detection target site where a polymorphism to be detected is generated is amplified according to a nucleic acid amplification method such as PCR in the presence of the labeled probe. Below, the present invention will be described using an example in which PCR is used as a nucleic acid amplification method, but the present invention is not limited thereto. Moreover, PCR conditions are not particularly limited and PCR can be carried out in a conventional manner.

In particular, PCR is carried out on a reaction mixture as described above that contains the genomic DNA and the labeled probe. The composition of the reaction mixture is not particularly limited and can be suitably arranged by a person skilled in the art and, for example, polymerases such as DNA polymerases, dNTPs such as dATP, dTTP, dCTP, dGTP and dUTP, buffers, various catalysts, primers, etc., may be contained therein in addition to the genomic DNA and the labeled probe.

Next, the dissociation of the amplification product (double-strand DNA) thus obtained as well as the hybridization between the single-strand DNA obtained by the dissociation and the labeled probe are performed. These can be carried out by, for example, changing the temperature of the reaction fluid.

The dissociation of the double-strand DNA can be carried out, for example, by heating. The heating temperature in this dissociation step is not particularly limited insofar as the amplification product can be dissociated and is, for example, 85 to 95° C. The heating time also is not particularly limited, and it is usually 1 second to 10 minutes and preferably 1 second to 5 minutes.

The hybridization between the dissociated single-strand DNA and the labeled probe can be carried out by, for example, lowering the heating temperature applied in the dissociation step after the dissociation step. Temperature conditions in this hybridization step are not particularly limited, and it is preferable that the temperature is lower than the Tm value of the labeled probe, for example, 40 to 50° C. Moreover, the duration of the treatment at such a temperature is not particularly limited and it is, for example, 1 to 600 seconds.

In the hybridization step, the volume and the concentration of each component of the reaction fluid are not particularly limited. For specific examples, the concentration of DNA in the reaction fluid is, for example, 0.01 to 1 μmol/L and preferably 0.1 to 0.5 μmol/L, and the concentration of the labeled probe is, for example, preferably within a range that satisfies the aforementioned proportion relative to the DNA, e.g., 0.001 to 10 μmol/L and preferably 0.001 to 1 μmol/L.

Then, the temperature of the reaction fluid is changed and a signal value that indicates the melting state of the hybridization product between the amplification product (the single-strand DNA) and the labeled probe is measured. In particular, the product of hybridization between the single-strand DNA and the labeled probe is heated by, for example, heating the reaction fluid, and a change in signal value associated with a temperature increase is measured. For example, when a probe in which the end cytosine is labeled (guanine-quenching probe) is used as described above, fluorescence is reduced (or quenched) if the probe is in a hybridized state with the single-strand DNA, and fluorescence is emitted if the probe is in a dissociated state. Therefore, for example, a hybridization product with reduced (or quenched) fluorescence is heated gradually, and an increase in the intensity of fluorescence associated with the temperature increase is measured.

The temperature range when measuring a change in the intensity of fluorescence is not particularly limited and, for example, the starting temperature is room temperature to 85° C. and preferably 25 to 70° C., and the end temperature is, for example, 40 to 105° C. The rate of temperature increase is not particularly limited and, for example, it is 0.1 to 20° C./second and preferably 0.3 to 5° C./second.

When two or more types of polymorphism are to be detected using two or more types of labeled probe, a change in signal resulting from each labeled probe is measured under conditions selected according to the labeling material of each labeled probe.

Next, the change in signal is analyzed to determine a Tm value. In particular, the extent of change in fluorescence intensity per unit time at respective temperatures, for example, is calculated based on the intensity of fluorescence thus obtained. For example, when the extent of change is (−d extent of increase in fluorescence intensity/dt), the temperature at which the lowest value is indicated can be determined as a Tm value. In addition, when the extent of change is (d extent of increase in fluorescence intensity/dt) for example, the highest point can be determined as a Tm value. When a probe that does not give any signal when alone and that gives a signal when forming a hybrid is used as a labeled probe

instead of a quenching probe, the extent of decrease in fluorescence intensity is measured instead.

Then, the polymorphism (genotype) in the desired detection target site is determined based on the Tm values. The results obtained from the Tm analysis show that, for example, a hybrid (match) that is fully complementary exhibits a Tm value, which indicates dissociation, higher than that of a hybrid (mismatch) that has one different nucleotide. Therefore, by determining in advance the Tm value of a hybrid that is fully complementary and the Tm value of a hybrid that has one different nucleotide in connection with a probe, the polymorphism in the desired detection target site can be determined. For example, when the polymorphism in the desired detection target site is X or Y and when a probe that is fully complementary to a detection target sequence whose detection target site is X is used, the base of the detection target site can be judged as X if the Tm value of a hybrid thus formed is the same as the Tm value of a fully complementary hybrid. On the other hand, if the Tm value of the hybrid thus formed is the same as the Tm value of a hybrid having one different nucleotide or is lower than the Tm value of a fully complementary hybrid, the base of the detection target site can be judged as Y.

Moreover, in the present invention, instead of the method described above in which the temperature of a reaction fluid is increased to heat a hybridization product and a change in signal associated with the temperature increase is measured, for example, a change in signal upon hybrid formation may be measured. That is, when a hybridization product is formed by lowering the temperature of a reaction fluid containing a probe, a change in signal associated with the temperature decrease may be measured.

The case where a labeled probe that gives a signal when alone and that does not give any signal when forming a hybrid (for example, a QProbe) is used will be described as a specific example. Fluorescence is emitted when single-strand DNA and the probe are in a dissociated state, and this fluorescence is reduced (or quenched) when a hybrid is formed due to a temperature decrease. Therefore, for example, the temperature of the reaction fluid may be gradually lowered, and the reduction in fluorescence intensity associated with the temperature decrease may be measured. On the other hand, when a labeled probe that does not give any signal when alone and that gives a signal when forming a hybrid is used, no fluorescence is emitted when single-strand DNA and the probe are in a dissociated state, and when a hybrid is formed due to a temperature decrease, fluorescence is emitted. Therefore, the temperature of the reaction fluid gradually may be lowered for example, and an increase in fluorescence intensity associated with the temperature decrease may be measured.

Polymorphism Detection Reagent

The polymorphism detection reagent of the present invention is a polymorphism detection reagent for detecting an immune-related gene polymorphism and contains a polymorphism detection probe of the present invention. A feature of the present invention is to contain an aforementioned polymorphism detection probe of the present invention, and any other configurations and conditions are not limited at all. The polymorphism detection reagent of the present invention also can be called as a probe kit for use, for example, in the detection of an immune-related gene polymorphism.

In the polymorphism detection reagent of the present invention, one type or two or more types of the polymorphism detection probe of the present invention may be present. When there are two or more types of the probe, a combination thereof is not particularly limited and examples of such a combination are as described above. Two or more types of the probe may be accommodated in, for example, separate containers, or may be accommodated in the same container in a mixed state since the detection of polymorphisms is possible in a single reaction system as described above. Moreover, when two or more types of probes are contained, it is preferable that each probe is labeled with a different labeling material. Accordingly, the use of different types of labeling materials enables respective probes to be detected even in a single reaction system. It is preferable that the labeling materials are, for example, materials of different detection wavelengths.

As described above, immune-related genes such as the FCGR3A gene, the FCGR2A gene, the IL-10 gene, the TNF α gene and the TNF β gene are each reported to have polymorphisms that are involved in the pharmaceutical effects of antibody drugs such as malignant lymphoma drugs (for example, trade name: rituxan) and breast cancer drugs (for example, trade name: herceptin), and such polymorphisms can all be detected with the use of the probes of the present invention. In connection with such polymorphisms, there may be a case where variants are detected in, for example, only one type and there may be a case where variants are detected in two or more types. Although the detection target polymorphisms in the present invention each show an association with the pharmaceutical effects of the aforementioned antibody drugs, they are believed to show their own respective specific characteristics. Thus, for example, the detection of a plurality of polymorphisms and a comprehensive evaluation of the results thereof will enable better diagnosis and medical treatment. Therefore, if two or more types of the probe of the present invention are contained in the polymorphism detection reagent or probe kit of the present invention, polymorphism detection that is intended for diagnosis, medical treatment and the like can be carried out in a simpler manner.

The detection reagent of the present invention further may contain a primer or a primer set for amplifying a region that includes a site to be detected in an immune-related gene. Examples of primer sets include those described above depending on the type of the probe of the present invention to be used. In particular, it is preferable to contain in any combination an FCGR3A probe and an FCGR3A primer set; an FCGR2A probe and an FCGR2A primer set; an IL-10 (−592) probe and an IL-10 (−592) primer set; an IL-10 (−819) probe and an IL-10 (−819) primer set; an IL-10 (−1082) probe and an IL-10 (−1082) primer set; an IL-10 (−3575) probe and an IL-10 (−3575) primer set; a TNF α probe and a TNF α primer set; and a TNF β probe and a TNF β primer set.

Combinations of the probes of the present invention are not particularly limited, and examples include those described above. Also, a combination of primers or primer sets can be determined according to the combination of the probes of the present invention.

The detection reagent of the present invention may contain, for example, components necessary for a nucleic acid amplification reaction in addition to those described above. Spe-

cific examples include polymerases such as DNA polymerases, dNTPs such as dATP, dTTP, dCTP, dGTP and dUTP, buffers, various catalysts, etc. Furthermore, the detection reagent of the present invention may be a detection reagent kit and may include instructions for use.

Next, the examples of the present invention shall be described. The present invention, however, is not limited by the following examples. The unit "%" refers to "w/v %".

EXAMPLES

Example 1

Detection of FCGR3A Polymorphism and IL-10 (−819) Polymorphism

Using probes of the present invention, FCGR3A polymorphisms and IL-10 (−819) polymorphisms were detected by a Tm analysis.

Blood was collected using EDTA blood collection tubes from 3 healthy subjects whose FCGR3A polymorphism and IL-10 (−819) polymorphism were known (Sample 1 to Sample 3). The FCGR3A polymorphism and the IL-10 (−819) polymorphism of each sample were as follows.

	FCGR3A Polymorphisms	IL-10 (−819) Polymorphisms
Sample 1	T/T	C/C
Sample 2	G/T	T/C
Sample 3	T/T	T/T

Each sample (10 μL) was mixed with 70 μL of the following test sample dilution 1, and the mixtures (10 μL each) were further mixed with 70 μL of the following test sample dilution 2. Each mixture (17 μL) was heated at 95° C. for 10 minutes and introduced into 46 μL of the following PCR reaction solution to carry out PCR. The PCR included a treatment at 95° C. for 60 seconds and then repeating 50 times a cycle of heating at 95° C. for 1 second and 62° C. for 15 seconds, followed by a treatment at 95° C. for 1 second and 40° C. for 60 seconds all performed by a thermal cycler. Then, the PCR reaction solution was heated from 40° C. to 75° C. at a rate of temperature increase of 1° C./3 seconds, and change in fluorescence intensity over time was measured (wavelengths: 515 to 555 nm, 585 to 700 nm).

Test Sample Dilution 1

10 mmol/L	Tris-HCl
0.1 mmol/L	EDTA
0.05%	NaN_3
0.3%	SDS

Test Sample Dilution 2

10 mmol/L	Tris-HCl
0.1 mmol/L	EDTA
0.05%	NaN_3

TABLE 17

(PCR reaction solution)	(Unit: μL)
Distilled water	28.02
10% NaN_3	0.23
20% BSA	0.5
50% Glycerol	2.5
10 × Gene Taq buffer*	5
2.5 mmol/L dNTPs	4
5 μmol/L FCGR3A probe	2
100 μmol/L FCGR3A F primer	0.5
100 μmol/L FCGR3A R primer	0.25
5 μmol/L IL-10 (−819) probe	2
100 μmol/L IL-10 (−819) F primer	0.5
100 μmol/L IL-10 (−819) R primer	0.25
5 U/μL Gene Taq FP*	0.25
Total	46 μL

*Trade name: Gene Taq FP, manufactured by Nippon Gene Co., Ltd.
FCGR3A probe (SEQ ID NO. 14)
5'-tcccaaAaagccccc-(BODIPY FL)-3'
FCGR3A F primer (SEQ ID NO. 77)
5'-tctgacttctacattccaaaagccacactcaaagac-3'
FCGR3A R primer (SEQ ID NO. 97)
5'-ctcctcccaactcaacttcccagtgtgat-3'
IL-10 (−819) probe (SEQ ID NO. 36)
5'-acagagatGttacatcacc-(TAMRA)-3'
IL-10 (−819) F primer (SEQ ID NO. 182)
5'-tgctggagatggtgtacagtagggtgagg-3'
IL-10 (−819) R primer (SEQ ID NO. 198)
5'-caccatgacccctaccgtctctattttatagtgagc-3'

FIG. **1** shows the results. FIG. **1** depicts graphs of a Tm analysis that shows the change in fluorescence intensity associated with temperature increase. In FIG. **1**, "(A)" shows the results of Sample 1, "(B)" shows the results of Sample 2 and "(C)" shows the results of Sample 3, and the upper row shows the results for the FCGR3A polymorphisms and the bottom row shows the results for the IL-10 (−819) polymorphisms.

In this example, a probe that perfectly matched the FCGR3A polymorphism (t) of the sense strand was used as an FCGR3A probe, and a probe that perfectly matched the IL-10 (−819) polymorphism (c) of the sense strand was used as an IL-10 (−819) probe. As a result, in the detection of an FCGR3A polymorphism, Sample 1 and Sample 3, which contain homozygotes (T/T), showed a peak only at 57.0° C., indicating a perfect match as shown in the upper row of FIG. **1**. On the other hand, Sample 2, which contains a heterozygote (G/T), showed a peak at 57.0° C., indicating a perfect match, as well as a peak at 48.0° C., indicating a single-base mismatch. Moreover, in the detection of an IL-10 (−819) polymorphism, Sample 1, which contains a homozygote (C/C), showed a peak only at 59.0° C., indicating a perfect match, and Sample 3, which contains a homozygote (T/T), showed a peak only at 52.5° C., indicating a mismatch, as shown in the bottom row of FIG. **1**. On the other hand, Sample 2, which contains a heterozygote (T/C), showed a peak at 59.0° C., indicating a perfect match, and a peak at 52.5° C., indicating a single-base mismatch. As can be understood from these results, using probes of the present invention, whether hybridization with a detection target sequence is of a

perfect match or a mismatch can be determined sufficiently, and two types of polymorphisms can be determined using a single reaction system.

Example 2

Detection of FCGR2A Polymorphism, IL-10 (−592) Polymorphism and TNF α Polymorphism

Using probes of the present invention, an FCGR2A polymorphism, an IL-10 (−592) polymorphism and TNF α (−308) polymorphisms were detected by a Tm analysis.

Blood was collected using an EDTA blood collection tube from a healthy subject whose FCGR2A polymorphism, IL-10 (−592) polymorphism and TNF α (−308) polymorphism were known (Sample 1). A plasmid having a TNF α gene whose TNF α (−308) polymorphism was a homozygote (A/A) was prepared (Sample 2). The FCGR2A polymorphism, the IL-10 (−592) polymorphism and the TNF α (−308) polymorphism of each sample were as follows.

	FCGR2A Polymorphism	IL-10 (−592) Polymorphism	TNFa Polymorphism
Sample 1	C/T	C/A	G/G
Sample 2	—	—	A/A

Sample 1 (10 μL) was mixed with 70 μL of the test sample dilution 1 described above, and the mixture (10 μL) was further mixed with 70 μL of the test sample dilution 2 described above. This mixture (17 μL) was heated at 95° C. for 10 minutes and introduced into 46 μL of the following PCR reaction solution to carry out PCR. On the other hand, 1 μL of Sample 2 (3.5 pg) was introduced into 46 μL of the following PCR reaction solution to carry out PCR. The PCR included a treatment at 95° C. for 60 seconds and then repeating 50 times a cycle of heating at 95° C. for 1 second and 62° C. for 15 seconds, followed by a treatment at 95° C. for 1 second and 40° C. for 60 seconds all performed by a thermal cycler. Then, the PCR reaction solution was heated from 40° C. to 75° C. at a rate of temperature increase of 1° C./3 seconds, and change in fluorescence intensity over time was measured (wavelengths: 450 to 480 nm, 515 to 555 nm, 585 to 700 nm).

TABLE 18

(PCR reaction solution)	(Unit: μL)
Distilled water	17.77
10% NaN_3	0.23
20% BSA	0.5
50% Glycerol	10
10 × Gene Taq buffer*	5
2.5 mmol/L dNTPs	4
5 μmol/L IL-b (-592) probe	2
100 μmol/L IL-10 (-592) F primer	0.5
100 μmol/L IL-10 (-592) R primer	0.25
5 μmol/L FCGR2A probe	2
100 μmol/L FCGR2A F primer	0.25

TABLE 18-continued

(PCR reaction solution)	(Unit: μL)
100 μmol/L FCGR2A R primer	0.5
5 μmol/L TNF α (-308) probe	2
100 μmol/L TNF α (-308) F primer	0.5
100 μmol/L TNF α (-308) R primer	0.25
5 U/μL Gene Tag FP*	0.25
Total	46 μL

Trade name: Gene Taq FP, manufactured by Nippon Gene Co., Ltd.
IL-10 (-592) probe (SEQ iD NO. 30)
5'-(Pacific Blue) -cttcctacagTacaggcg-P-3'
IL-10(-592) F primer (SEQ ID NO. 148)
5'-ggtaaaggagcctggaacacatcctgtgac-3'
IL-10(-592) Rprimer (SEQ ID NO. 167)
5'- agcccttccattttactttccagagactggc-3'
FCGR2A probe (SEQ ID NO. 23)
5'-ttctcccAtttggatccc-(BODIPY FL)-3'
FCGR2A F primer (SEQ ID NO. 132)
5'-ctgtggtttgcttgtgggatggagaagg-3'
FCGR2A R primer (SEQ ID NO. 38)
5'-aggtcacattcttccagaatggaaaatcccagaaattc-3'
TNF α (-308) probe (SEQ ID NO. 64)
5'-ccgtccCcatgccc-(TAMRA)-3'
TNF α (-308) F primer (SEQ ID NO. 277)
5'-cctggtccccaaaagaaatggaggcaatagg-3'
TNF α (-308) R primer (SEQ ID NO. 293)
5'-ccactgactgatttgtgtgtaggaccctgg-3'

FIG. **2** shows the results. FIG. **2** depicts graphs of a Tm analysis that shows the change in fluorescence intensity associated with the temperature increase. In FIG. **2**, "(A)" shows the results of Sample 1, "(B)" shows the results of Sample 2, the upper row shows the results for the IL-10 (−592) polymorphism, the mid row shows the results for the FCGR2A polymorphism, and the bottom row shows the results for the TNF α (−308) polymorphisms.

In this example, a probe that perfectly matched the IL-10 (−592) polymorphism (a) of the sense strand was used as an IL-10 (−592) probe, a probe that perfectly matched the FCGR2A polymorphism (t) of the sense strand was used as an FCGR2A probe, and a probe that perfectly matched the TNF α (−308) polymorphism (g) of the sense strand was used as a TNF α (−308) probe. As a result, in the detection of an IL-10 (−592) polymorphism, Sample 1, which contains a heterozygote (C/A), showed a peak at 58.0° C., indicating a perfect match, as well as a peak at 50.0° C., indicating a single-base mismatch, as shown in the upper row of FIG. **2**. Moreover, in the detection of an FCGR2A polymorphism, Sample 1, which contains a heterozygote (C/T), showed a peak at 57.0° C., indicating a perfect match, as well as a peak at 48.0° C., indicating a single-base mismatch, as shown in the mid row of FIG. **2**. Furthermore, in the detection of an TNF α (−308) polymorphism, Sample 1, which contains a homozygote (G/G), showed a peak only at 61.0° C., indicating a perfect match, and Sample 2, which contains a homozygote (A/A), showed a peak only at 49.0° C., indicating a single-base mismatch, as shown in the bottom row of FIG. **2**. As can be understood from the results, using probes of the present invention, whether hybridization with a detection target sequence is of a perfect match or a mismatch can be determined sufficiently, and three types of polymorphisms can be determined using a single reaction system.

Example 3

Detection of IL-10 (−1082) Polymorphism and IL-10 (−3575) Polymorphism

Using probes of the present invention, IL-10 (−1082) polymorphisms and IL-10 (−3575) polymorphisms were detected by a Tm analysis.

Blood was collected using an EDTA blood collection tube from a healthy subject whose IL-10 (−1082) polymorphism and IL-10 (−3575) polymorphism were known (Sample 1). Moreover, using a GFX Genomic Blood DNA Purification Kit (trade name, manufactured by GE Healthcare Bioscience), a genome whose IL-10 (−1082) polymorphism and IL-10 (−3575) polymorphism were known was purified, and diluted 10 fold to give Sample 2. In addition, a synthetic DNA whose IL-10 (−3575) polymorphism was a homozygote (A/A) was prepared (Sample 3). The IL-10 (−1082) polymorphism and the IL-10 (−3575) polymorphism of each sample were as follows.

	IL-10 (−1082) Polymorphism	IL-10 (−3575) Polymorphism
Sample 1	A/A	T/T
Sample 2	A/G	T/T
Sample 3	—	A/A

Sample 1 (10 μL) was mixed with 70 μL of the test sample dilution 1 described above, and the mixture (10 μL) was further mixed with 70 μL of the test sample dilution 2 described above. This mixture (17 μL) was heated at 95° C. for 10 minutes and introduced into 46 μL of the following PCR reaction solution to carry out PCR. On the other hand, 1 μL of Sample 2 and 1 μL of Sample 3 (3.5 pg) each were introduced into 46 μL of the following PCR reaction solution to carry out PCR. The PCR included a treatment at 95° C. for 60 seconds and then repeating 50 times a cycle of heating at 95° C. for 1 second and 64° C. for 15 seconds, followed by a treatment at 95° C. for 1 second and 40° C. for 60 seconds all performed by a thermal cycler. Then, the PCR reaction solution was heated from 40° C. to 75° C. at a rate of temperature increase of 1° C./3 seconds, and change in fluorescence intensity over time was measured (wavelengths: 515 to 555 nm, 585 to 700 nm).

TABLE 19

(PCR reaction solution)	(Unit: μL)
Distilled water	20.27
10% NaN_3	0.23
20% BSA	0.5
50% Glycerol	10
10 × Gene Taq buffer*	5
2.5 mmol/L dNTPs	4
100 mmol/L $MgCl_2$	0.25
5 μmol/L IL-10 (−1082) probe	2
100 μmol/L IL-10 (−1082) F primer	0.5
100 μmol/L IL-10 (−1082) R primer	0.25
5 μmol/L IL-10 (−3575) probe	2
100 μmol/L IL-10 (−3575) F primer	0.25
100 μmol/L IL-10 (−3575) R primer	0.5
5 U/μL Gene Tag FP*	0.25
Total	46 μL

*Trade name: Gene Taq FP, manufactured by Nippon Gene Co., Ltd.

IL-10 (−1082) probe (SEQ ID NO. 47)
5'-(BODIPY FL)-ccctacttccccCtccc-P- 3'
IL-10(−1082) F primer (SEQ ID NO. 213)
5'-ccgcaacccaactggctctccttac-3'
IL-10(−1082) R primer (SEQ ID NO. 227)
5'-ggattccatggaggctggataggaggtcc-3'
IL-10(−3575) probe (SEQ ID NO. 57)
5'-(TAMRA)-cccactggaaaaatTcattt-P-3'
IL-10(−3575) F primer (SEQ ID NO. 244)
5'-ggatggaagaagagaggtattccccttcccac-3'
IL-10(−3575) R primer (SEQ ID NO. 260)
5'-ccagtttgccctcaagcccagatgc-3'

FIG. **3** shows the results. FIG. **3** depicts graphs of a Tm analysis that shows the change in fluorescence intensity associated with the temperature increase. In FIG. **3**, "(A)" shows the results of Sample 1, "(B)" shows the results of Sample 2, "(C)" shows the results of Sample 3, the upper row shows the results for the IL-10 (−1082) polymorphisms, and the bottom row shows the results for the IL-10 (−3575) polymorphisms.

In this example, a probe that perfectly matched the IL-10 (−1082) polymorphism (g) of the sense strand was used as an IL-10 (−1082) probe, and a probe that perfectly matched the IL-10 (−3575) polymorphism (a) of the antisense strand was used as an IL-10 (−3575) probe. This is synonymous with perfectly matching the IL-10 (−3575) polymorphism (t) of the sense strand. As a result, in the detection of an IL-10 (−1082) polymorphism, Sample 1, which contains a homozygote (A/A), showed a peak only at 49.0° C., indicating a mismatch, and on the other hand, Sample 2, which contains a heterozygote (A/G), showed a peak at 60.0° C., indicating a perfect match, as well as a peak at 49.0° C., indicating a single-base mismatch, as shown in the upper row of FIG. **3**. Moreover, in the detection of an IL-10 (−3575) polymorphism, Sample 1 and Sample 2, which contain homozygotes (T/T), showed a peak only at 56.0° C., indicating a perfect match, and Sample 3, which contains a homozygote (A/A), showed a peak only at 49.0° C., indicating a mismatch, as shown in the bottom row of FIG. **3**. As can be understood from the results, using probes of the present invention, whether hybridization with a detection target sequence is of a perfect match or a mismatch can be sufficiently determined, and two types of polymorphisms can be determined using a single reaction system.

As can be understood from the results presented above, using the probes of the present invention, whether hybridization with a detection target sequence is of a perfect match or of a mismatch can be fully determined. Therefore, according to the present invention, whether a polymorphism in a detection target site is a polymorphism (X) or a polymorphism (Y) can be distinguished with good accuracy. Moreover, since it is possible to determine between a perfect match and a mismatch, it is possible to determine, for example, whether a polymorphism to be detected is a homozygote (X/X or Y/Y) or a heterozygote (X/Y) and, in addition, whether the polymorphism is a homozygote (X/X) or a homozygote (Y/Y). Furthermore, it is possible to determine two or more types of polymorphisms in one reaction system.

INDUSTRIAL APPLICABILITY

As described above, in connection with the immune-related genes FCGR3A, FCGR2A, IL-10, TNF α and TNF β, it is possible according to the present invention to distinguish polymorphisms in which only one base is different. Therefore, by applying the probes of the present invention to, for example, a Tm analysis or the like, polymorphism detection can be carried out in a simple manner. Moreover, according to the present invention, even when two or more types of probes are concomitantly present in one reaction system, corresponding gene polymorphisms can be distinguished by the respective probes. Therefore, a plurality of polymorphisms can be detected using one reaction system. Thus, according to the present invention, since polymorphisms of immune-related genes can be readily distinguished, the results of detection can be reflected also in, for example, the therapeutic administration of antibody drugs as described above. Therefore, the present invention is particularly useful in the medical field and like technical fields.

SEQUENCE LISTING

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agtattttca tcataattct gacttctaca ttccaaaagc cacactcaaa gacagcggct 180

cctacttctg caggggggctt kttgggagta aaaatgtgtc ttcagagact gtgaacatca 240

ccatcactca aggtgagaca tgtgccaccc tggaatgccc agggacgcct gtgtgtggaa 300

cctgcaatca cactgggaag ttgagttggg aggagattcc tgattcttac acgcacttct 360

tcatatgtgg ttccctcctg gtgatcacca ggaggtcccc a 401

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<213> ORGANISM: Homo sapiens

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tgtagcctat gtttcctgtg cagtggtaat caccactgtg actgtggttt gcttgtggga 180

tggagaaggt gggatccaaa ygggagaatt tctgggattt tccattctgg aagaatgtga 240

ccttgaccag aggcttgtcc ttccagctgt ggcacctcag catgatggtt tctccctcct 300

ggaactccag gtgaggggtc tggagcacca gccattctga aagacacaaa tatgataaga 360

aaaagttgta aggatagatt ccaagggttt ttcagtctca gaggtacgtt actcacagaa 420

cttgacatga tgtctggcag acagaaatga agatgcttca tgacagatgt gagcattctc 480

ttataggcaa tatatggtat t 501

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acaggtgatg taacatctct gtgcctcagt ttgctcacta taaaatagag acggtagggg 120

tcatggtgag cactacctga ctagcatata agaagctttc agcaagtgca gactactctt 180

acccacttcc cccaagcaca gttggggtgg gggacagctg aagaggtgga aacatgtgcc 240

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tgagaatcct aatgaaatcg gggtaaagga gcctggaaca catcctgtga ccccgcctgt 300

mctgtaggaa gccagtctct ggaaagtaaa atggaagggc tgcttgggaa ctttgaggat 360

atttagccca ccccctcatt tttacttggg gaaactaagg cccagagacc taaggtgact 420

gcctaagtta gcaaggagaa gtcttgggta ttcatcccag gttgggggga cccaattatt 480

tctcaatccc attgtattct ggaatgggca atttgtccac gtcactgtga cctaggaaca 540

cgcgaatgag aacccacagc tgagggcctc tgcgcacaga acagctgttc tccccaggaa 600

a 601

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ctaaggcttc tttgggaagg ggaagtaggg ataggtaaga ggaaagtaag ggacctccta 180

tccagcctcc atggaatcct gacttctttt ccttgttatt tcaacttctt ccaccccatc 240

ttttaaactt tagactccag ccacagaagc ttacaactaa aagaaactct aaggccaatt 300

taatccaagg tttcattcta tgtgctggag atggtgtaca gtagggtgag gaaaccaaat 360

tctcagttgg cactggtgta cccttgtaca ggtgatgtaa yatctctgtg cctcagtttg 420

ctcactataa aatagagacg gtaggggtca tggtgagcac tacctgacta gcatataaga 480

agctttcagc aagtgcagac tactcttacc cacttccccc aagcacagtt ggggtggggg 540

acagctgaag aggtggaaac atgtgcctga gaatcctaat gaaatcgggg taaaggagcc 600

tggaacacat cctgtgaccc cgcctgtact gtaggaagcc agtctctgga aagtaaaatg 660

gaagggctgc ttgggaactt tgaggatatt tagcccaccc cctcattttt acttggggaa 720

actaaggccc agagacctaa ggtgactgcc taagttagca aggagaagtc ttgggtattc 780

atcccaggtt gggggggaccc a 801

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<223> OTHER INFORMATION: n stands for any base
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<223> OTHER INFORMATION: n stands for any base

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ccaggcctcc tgcacctagg tcagtgttcc tcccagttac agtctaaact ggaatggcag 180

gcaaagcccc tgtggaaggg gaaggtgaag ctcaaatcaa agctcnncca gagactttcc 240

agatatctga agaagtcctg atgtcactgc cccggtcctt ccccaggtag agcaacactc 300

ctcgccgcaa cccaactggc tctccttact ttctacacac acacacacac acacacacac 360

acacacacac acacacacaa atccaagaca acactactaa ggcttctttg ggarggggaa 420

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gtagggatag gtaagaggaa agtaagggac ctcctatcca gcctccatgg aatcctgact 480

tcttttcctt gttatttcaa cttcttccac cccatctttt aaactttaga ctccagccac 540

agaagcttac aactaaaaga aactctaagg ccaatttaat ccaaggtttc attctatgtg 600

ctggagatgg tgtacagtag ggtgaggaaa ccaaattctc agttggcact ggtgtaccct 660

tgtacaggtg atgtaatatc tctgtgcctc agtttgctca ctataaaata gagacggtag 720

gggtcatggt gagcactacc tgactagcat ataagaagtt tcagcaagtg ggggatcctc 780

tagagtcgcg acctcagcan nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 840

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gattttggat tca 913

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<400> SEQUENCE: 6

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gaggtattcc ccttcccaca awcttctgat ttcccagtac atcccccact ggaaaaatwc 180

atttaaaatc agtataataa gcattgattr gatgcctact atgcatctgg gcttgagggc 240

aaactggact caggcctttt ggcctcaaga agctcacagt gtgagagtgg catttgtgtc 300

ctcttgaaat tcacaggact aaattgtgcc caggctgaca ttctatccat ccataggtgc 360

ctgccttctc acttccctct cttcatgggc tcttgccttg taccaaaatc caaacccaaa 420

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caggcttgtc cctgctaccc ccacccagcc tttcctgagg cctcaagcct gccaccaagc 180

ccccagctcc ttctccccgc agggacccaa acacaggcct caggactcaa cacagctttt 240

ccctccaacc ccgttttctc tccctcaagg actcagcttt ctgaagcccc tcccagttct 300

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gggtcctaca cacaaatcag tcagtggccc agaagacccc cctcggaatc ggagcaggga 480

ggatggggag tgtgaggggt atccttgatg cttgtgtgtc cccaactttc caaatccccg 540

cccccgcgat ggagaagaaa ccgagacaga aggtgcaggg cccactaccg cttcctccag 600

atgagctcat gggtttctcc accaaggaag ttttccgctg gttgaatgat tctttccccg 660

ccctcctctc gccccaggga catataaagg cagttgttgg cacacccagc cagcagacgc 720

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ctgaaaacaa ccctcagacg c 801

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tttactccca aaaagccccc 20

<210> SEQ ID NO 10
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tactcccaaa aagccccc 18

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ctcccaaaaa gccccc 16

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cccaaaaagc cccc 14

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ccaaaaagcc ccc 13

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cagaaattct cccatttgga tccc 24

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<213> ORGANISM: Artificial
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gaaattctcc catttggatc cc 22

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aaattctccc atttggatcc c 21

<210> SEQ ID NO 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 21

aattctccca tttggatccc 20

<210> SEQ ID NO 22
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 22

attctcccat ttggatccc 19

<210> SEQ ID NO 23
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

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ttctcccatt tggatccc 18

<210> SEQ ID NO 24
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 24

tctcccattt ggatccc 17

<210> SEQ ID NO 25
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<213> ORGANISM: Artificial
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cttcctacag tacaggcggg g 21

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<400> SEQUENCE: 28

cttcctacag tacaggcggg 20

<210> SEQ ID NO 29
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 29

cttcctacag tacaggcgg 19

<210> SEQ ID NO 30
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 30

cttcctacag tacaggcg 18

<210> SEQ ID NO 31
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<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 31

cttcctacag tacaggc 17

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 32

cttcctacag tacagg 16

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<210> SEQ ID NO 36
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<212> TYPE: DNA
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<400> SEQUENCE: 36

acagagatgt tacatcacc 19

<210> SEQ ID NO 37
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cagagatgtt acatcacc 18

<210> SEQ ID NO 38
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<220> FEATURE:
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<400> SEQUENCE: 38

agagatgtta catcacc 17

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<220> FEATURE:
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<400> SEQUENCE: 39

gagatgttac atcacc 16

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ccctacttcc ccctcccaaa ga 22

<210> SEQ ID NO 43
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ccctacttcc ccctcccaa 19

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ccctacttcc ccctccca 18

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<223> OTHER INFORMATION: probe

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ccctacttcc ccctccc 17

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ccctacttcc ccctcc 16

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<220> FEATURE:
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<400> SEQUENCE: 51

cccactggaa aaattcattt aaaatc 26

<210> SEQ ID NO 52
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 52

cccactggaa aaattcattt aaaat 25

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<400> SEQUENCE: 55

cccactggaa aaattcattt aa 22

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<400> SEQUENCE: 56

cccactggaa aaattcattt a 21

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<400> SEQUENCE: 57

cccactggaa aaattcattt 20

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<400> SEQUENCE: 58

cccactggaa aaattcatt 19

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<400> SEQUENCE: 59

cccactggaa aaattcat 18

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<223> OTHER INFORMATION: probe

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cccactggaa aaattca 17

<210> SEQ ID NO 61
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<220> FEATURE:
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cccactggaa aaattc 16

<210> SEQ ID NO 62
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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ccccgtcccc atgccc 16

<210> SEQ ID NO 63
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 63

cccgtcccca tgccc 15

<210> SEQ ID NO 64
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 64

ccgtccccat gccc 14

<210> SEQ ID NO 65
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 65

cgtccccatg ccc 13

<210> SEQ ID NO 66
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 66

gtccccatgc cc 12

<210> SEQ ID NO 67
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 67

tcatcataat tctgacttct acattccaaa agccacactc aaagac 46

<210> SEQ ID NO 68
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 68

catcataatt ctgacttcta cattccaaaa gccacactca aagac 45

<210> SEQ ID NO 69
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<212> TYPE: DNA
<213> ORGANISM: Artificial
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atcataattc tgacttctac attccaaaag ccacactcaa agac 44

<210> SEQ ID NO 70
<211> LENGTH: 43
<212> TYPE: DNA
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tcataattct gacttctaca ttccaaaagc cacactcaaa gac 43

<210> SEQ ID NO 71
<211> LENGTH: 42
<212> TYPE: DNA
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<400> SEQUENCE: 71

cataattctg acttctacat tccaaaagcc acactcaaag ac 42

<210> SEQ ID NO 72
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 72

ataattctga cttctacatt ccaaaagcca cactcaaaga c 41

<210> SEQ ID NO 73
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<400> SEQUENCE: 73

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taattctgac ttctacattc caaaagccac actcaaagac 40

<210> SEQ ID NO 74
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<400> SEQUENCE: 74

aattctgact tctacattcc aaaagccaca ctcaaagac 39

<210> SEQ ID NO 75
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<212> TYPE: DNA
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<400> SEQUENCE: 75

attctgactt ctacattcca aaagccacac tcaaagac 38

<210> SEQ ID NO 76
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<212> TYPE: DNA
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<400> SEQUENCE: 76

ttctgacttc tacattccaa aagccacact caaagac 37

<210> SEQ ID NO 77
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 77

tctgacttct acattccaaa agccacactc aaagac 36

<210> SEQ ID NO 78
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 78

ctgacttcta cattccaaaa gccacactca aagac 35

<210> SEQ ID NO 79
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<212> TYPE: DNA
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tgacttctac attccaaaag ccacactcaa agac 34

<210> SEQ ID NO 80
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<212> TYPE: DNA
<213> ORGANISM: Artificial

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<220> FEATURE:
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<400> SEQUENCE: 80

gacttctaca ttccaaaagc cacactcaaa gac 33

<210> SEQ ID NO 81
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 81

acttctacat tccaaaagcc acactcaaag ac 32

<210> SEQ ID NO 82
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 82

cttctacatt ccaaaagcca cactcaaaga c 31

<210> SEQ ID NO 83
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 83

ttctacattc caaaagccac actcaaagac 30

<210> SEQ ID NO 84
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 84

tctacattcc aaaagccaca ctcaaagac 29

<210> SEQ ID NO 85
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 85

ctacattcca aaagccacac tcaaagac 28

<210> SEQ ID NO 86
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 86

tacattccaa aagccacact caaagac 27

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<210> SEQ ID NO 87
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial
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aatcaggaat ctcctcccaa ctcaacttcc cagtgtgat 39

<210> SEQ ID NO 88
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial
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atcaggaatc tcctcccaac tcaacttccc agtgtgat 38

<210> SEQ ID NO 89
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 89

tcaggaatct cctcccaact caacttccca gtgtgat 37

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<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 90

caggaatctc ctcccaactc aacttcccag tgtgat 36

<210> SEQ ID NO 91
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 91

aggaatctcc tcccaactca acttcccagt gtgat 35

<210> SEQ ID NO 92
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 92

ggaatctcct cccaactcaa cttcccagtg tgat 34

<210> SEQ ID NO 93
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 93

gaatctcctc ccaactcaac ttcccagtgt gat 33

<210> SEQ ID NO 94
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 94

aatctcctcc caactcaact tcccagtgtg at 32

<210> SEQ ID NO 95
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 95

atctcctccc aactcaactt cccagtgtga t 31

<210> SEQ ID NO 96
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 96

tctcctccca actcaacttc ccagtgtgat 30

<210> SEQ ID NO 97
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 97

ctcctcccaa ctcaacttcc cagtgtgat 29

<210> SEQ ID NO 98
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 98

tcctcccaac tcaacttccc agtgtgat 28

<210> SEQ ID NO 99
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 99

cctcccaact caacttccca gtgtgat 27

<210> SEQ ID NO 100

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<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 100

ctcccaactc aacttcccag tgtgat 26

<210> SEQ ID NO 101
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 101

tcccaactca acttcccagt gtgat 25

<210> SEQ ID NO 102
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 102

cccaactcaa cttcccagtg tgat 24

<210> SEQ ID NO 103
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 103

ccaactcaac ttcccagtgt gat 23

<210> SEQ ID NO 104
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 104

cctctggtca aggtcacatt cttccagaat ggaaaatccc agaaattc 48

<210> SEQ ID NO 105
<211> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 105

ctctggtcaa ggtcacattc ttccagaatg gaaaatccca gaaattc 47

<210> SEQ ID NO 106
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 106

tctggtcaag gtcacattct tccagaatgg aaaatcccag aaattc 46

<210> SEQ ID NO 107
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 107

ctggtcaagg tcacattctt ccagaatgga aaatcccaga aattc 45

<210> SEQ ID NO 108
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 108

tggtcaaggt cacattcttc cagaatggaa aatcccagaa attc 44

<210> SEQ ID NO 109
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 109

ggtcaaggtc acattcttcc agaatggaaa atcccagaaa ttc 43

<210> SEQ ID NO 110
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 110

gtcaaggtca cattcttcca gaatggaaaa tcccagaaat tc 42

<210> SEQ ID NO 111
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 111

tcaaggtcac attcttccag aatggaaaat cccagaaatt c 41

<210> SEQ ID NO 112
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 112

caaggtcaca ttcttccaga atggaaaatc ccagaaattc 40

<210> SEQ ID NO 113
<211> LENGTH: 39
<212> TYPE: DNA

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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 113

aaggtcacat tcttccagaa tggaaaatcc cagaaattc 39

<210> SEQ ID NO 114
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 114

aggtcacatt cttccagaat ggaaaatccc agaaattc 38

<210> SEQ ID NO 115
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 115

ggtcacattc ttccagaatg gaaaatccca gaaattc 37

<210> SEQ ID NO 116
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 116

gtcacattct tccagaatgg aaaatcccag aaattc 36

<210> SEQ ID NO 117
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 117

tcacattctt ccagaatgga aaatcccaga aattc 35

<210> SEQ ID NO 118
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 118

cacattcttc cagaatggaa aatcccagaa attc 34

<210> SEQ ID NO 119
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 119

acattcttcc agaatggaaa atcccagaaa ttc 33

<210> SEQ ID NO 120
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 120

cattcttcca gaatggaaaa tcccagaaat tc 32

<210> SEQ ID NO 121
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 121

attcttccag aatggaaaat cccagaaatt c 31

<210> SEQ ID NO 122
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 122

accactgtga ctgtggtttg cttgtgggat ggagaagg 38

<210> SEQ ID NO 123
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 123

ccactgtgac tgtggtttgc ttgtgggatg gagaagg 37

<210> SEQ ID NO 124
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 124

cactgtgact gtggtttgct tgtgggatgg agaagg 36

<210> SEQ ID NO 125
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 125

actgtgactg tggtttgctt gtgggatgga gaagg 35

<210> SEQ ID NO 126
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:

<223> OTHER INFORMATION: primer

<400> SEQUENCE: 126

ctgtgactgt ggtttgcttg tgggatggag aagg 34

<210> SEQ ID NO 127
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 127

tgtgactgtg gtttgcttgt gggatggaga agg 33

<210> SEQ ID NO 128
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 128

gtgactgtgg tttgcttgtg ggatggagaa gg 32

<210> SEQ ID NO 129
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 129

tgactgtggt ttgcttgtgg gatggagaag g 31

<210> SEQ ID NO 130
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 130

gactgtggtt tgcttgtggg atggagaagg 30

<210> SEQ ID NO 131
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 131

actgtggttt gcttgtggga tggagaagg 29

<210> SEQ ID NO 132
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 132

ctgtggtttg cttgtgggat ggagaagg 28

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<210> SEQ ID NO 133
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 133

tgtggtttgc ttgtgggatg gagaagg 27

<210> SEQ ID NO 134
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 134

gtggtttgct tgtgggatgg agaagg 26

<210> SEQ ID NO 135
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 135

tggtttgctt gtgggatgga gaagg 25

<210> SEQ ID NO 136
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 136

ggtttgcttg tgggatggag aagg 24

<210> SEQ ID NO 137
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 137

gtttgcttgt gggatggaga agg 23

<210> SEQ ID NO 138
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 138

atgaaatcgg ggtaaaggag cctggaacac atcctgtgac 40

<210> SEQ ID NO 139
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

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<400> SEQUENCE: 139

tgaaatcggg gtaaaggagc ctggaacaca tcctgtgac 39

<210> SEQ ID NO 140
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 140

gaaatcgggg taaaggagcc tggaacacat cctgtgac 38

<210> SEQ ID NO 141
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 141

aaatcggggt aaaggagcct ggaacacatc ctgtgac 37

<210> SEQ ID NO 142
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 142

aatcggggta aaggagcctg gaacacatcc tgtgac 36

<210> SEQ ID NO 143
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 143

atcggggtaa aggagcctgg aacacatcct gtgac 35

<210> SEQ ID NO 144
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 144

tcggggtaaa ggagcctgga acacatcctg tgac 34

<210> SEQ ID NO 145
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 145

cggggtaaag gagcctggaa cacatcctgt gac 33

<210> SEQ ID NO 146
<211> LENGTH: 32

<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 146

ggggtaaagg agcctggaac acatcctgtg ac 32

<210> SEQ ID NO 147
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 147

gggtaaagga gcctggaaca catcctgtga c 31

<210> SEQ ID NO 148
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 148

ggtaaaggag cctggaacac atcctgtgac 30

<210> SEQ ID NO 149
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 149

gtaaaggagc ctggaacaca tcctgtgac 29

<210> SEQ ID NO 150
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 150

taaaggagcc tggaacacat cctgtgac 28

<210> SEQ ID NO 151
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 151

aaaggagcct ggaacacatc ctgtgac 27

<210> SEQ ID NO 152
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 152

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aaggagcctg gaacacatcc tgtgac 26

<210> SEQ ID NO 153
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

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aggagcctgg aacacatcct gtgac 25

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ggagcctgga acacatcctg tgac 24

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ccaagcagcc cttccatttt actttccaga gactggc 37

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caagcagccc ttccatttta ctttccagag actggc 36

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gcagcccttc cattttactt tccagagact ggc 33

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cttccatttt actttccaga gactggc 27

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tatgtgctgg agatggtgta cagtagggtg agg 33

<210> SEQ ID NO 179

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tgtgctggag atggtgtaca gtagggtgag g 31

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gtgctggaga tggtgtacag tagggtgagg 30

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tgctggagat ggtgtacagt agggtgagg 29

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gctggagatg gtgtacagta gggtgagg 28

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ctggagatgg tgtacagtag ggtgagg 27

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tggagatggt gtacagtagg gtgagg 26

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ggagatggtg tacagtaggg tgagg 25

<210> SEQ ID NO 187
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gagatggtgt acagtagggt gagg 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 190

gtagtgctca ccatgacccc taccgtctct attttatagt gagc 44

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tagtgctcac catgacccct accgtctcta ttttatagtg agc 43

<210> SEQ ID NO 192
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<213> ORGANISM: Artificial
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<400> SEQUENCE: 192

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 193

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tgctcaccat gacccctacc gtctctattt tatagtgagc 40

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<210> SEQ ID NO 196
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<400> SEQUENCE: 196

ctcaccatga cccctaccgt ctctatttta tagtgagc 38

<210> SEQ ID NO 197
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tcaccatgac ccctaccgtc tctattttat agtgagc 37

<210> SEQ ID NO 198
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<212> TYPE: DNA
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caccatgacc cctaccgtct ctattttata gtgagc 36

<210> SEQ ID NO 199
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accatgaccc ctaccgtctc tattttatag tgagc 35

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<400> SEQUENCE: 200

ccatgacccc taccgtctct attttatagt gagc 34

<210> SEQ ID NO 201
<211> LENGTH: 33
<212> TYPE: DNA
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<400> SEQUENCE: 201

catgaccct accgtctcta ttttatagtg agc 33

<210> SEQ ID NO 202
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atgaccccta ccgtctctat tttatagtga gc 32

<210> SEQ ID NO 203
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<400> SEQUENCE: 203

tgacccctac cgtctctatt ttatagtgag c 31

<210> SEQ ID NO 204
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gacccctacc gtctctattt tatagtgagc 30

<210> SEQ ID NO 205
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<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 205

acccctaccg tctctatttt atagtgagc 29

<210> SEQ ID NO 206
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ctcctcgccg caacccaact ggctctcctt ac 32

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<212> TYPE: DNA
<213> ORGANISM: Artificial
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tcctcgccgc aacccaactg gctctcctta c 31

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<210> SEQ ID NO 209
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<212> TYPE: DNA
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<400> SEQUENCE: 209

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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 210

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<212> TYPE: DNA
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cgccgcaacc caactggctc tccttac 27

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<212> TYPE: DNA
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gccgcaaccc aactggctct ccttac 26

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<211> LENGTH: 25
<212> TYPE: DNA
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<400> SEQUENCE: 213

ccgcaaccca actggctctc cttac 25

<210> SEQ ID NO 214
<211> LENGTH: 24
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 214

cgcaacccaa ctggctctcc ttac 24

<210> SEQ ID NO 215
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gcaacccaac tggctctcct tac 23

<210> SEQ ID NO 216
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<212> TYPE: DNA
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caacccaact ggctctcctt ac 22

<210> SEQ ID NO 217
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 217

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 218

aagaagtcag gattccatgg aggctggata ggaggtcc 38

<210> SEQ ID NO 219
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 219

agaagtcagg attccatgga ggctggatag gaggtcc 37

<210> SEQ ID NO 220
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 220

gaagtcagga ttccatggag gctggatagg aggtcc 36

<210> SEQ ID NO 221
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 221

aagtcaggat tccatggagg ctggatagga ggtcc 35

<210> SEQ ID NO 222
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<212> TYPE: DNA
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<220> FEATURE:
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agtcaggatt ccatggaggc tggataggag gtcc 34

<210> SEQ ID NO 223
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<212> TYPE: DNA
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<220> FEATURE:
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gtcaggattc catggaggct ggataggagg tcc 33

<210> SEQ ID NO 224
<211> LENGTH: 32
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tcaggattcc atggaggctg gataggaggt cc 32

<210> SEQ ID NO 225
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<212> TYPE: DNA
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caggattcca tggaggctgg ataggaggtc c 31

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<212> TYPE: DNA
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ggattccatg gaggctggat aggaggtcc 29

<210> SEQ ID NO 228
<211> LENGTH: 28
<212> TYPE: DNA
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<400> SEQUENCE: 228

gattccatgg aggctggata ggaggtcc 28

<210> SEQ ID NO 229
<211> LENGTH: 27
<212> TYPE: DNA
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<210> SEQ ID NO 230
<211> LENGTH: 26
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<400> SEQUENCE: 230

ttccatggag gctggatagg aggtcc 26

<210> SEQ ID NO 231
<211> LENGTH: 25
<212> TYPE: DNA
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tccatggagg ctggatagga ggtcc 25

<210> SEQ ID NO 232
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<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 232

ccatggaggc tggataggag gtcc 24

<210> SEQ ID NO 233
<211> LENGTH: 23
<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 233

catggaggct ggataggagg tcc 23

<210> SEQ ID NO 234
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 234

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<210> SEQ ID NO 235
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<212> TYPE: DNA
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<400> SEQUENCE: 235

gaggagcagg gatggaagaa gagaggtatt ccccttccca c 41

<210> SEQ ID NO 236
<211> LENGTH: 40
<212> TYPE: DNA
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<210> SEQ ID NO 237
<211> LENGTH: 39
<212> TYPE: DNA
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<220> FEATURE:
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ggagcaggga tggaagaaga gaggtattcc ccttcccac 39

<210> SEQ ID NO 238
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<220> FEATURE:
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<400> SEQUENCE: 238

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<210> SEQ ID NO 239
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agcagggatg gaagaagaga ggtattcccc ttcccac 37

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<220> FEATURE:
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gcagggatgg aagaagagag gtattcccct tcccac 36

<210> SEQ ID NO 241
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<400> SEQUENCE: 241

cagggatgga agaagagagg tattcccctt cccac 35

<210> SEQ ID NO 242
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 242

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<210> SEQ ID NO 243
<211> LENGTH: 33
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 243

gggatggaag aagagaggta ttccccttcc cac 33

<210> SEQ ID NO 244
<211> LENGTH: 32
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<220> FEATURE:
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<400> SEQUENCE: 244

ggatggaaga agagaggtat tcccccttccc ac 32

<210> SEQ ID NO 245
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 245

gatggaagaa gagaggtatt ccccttccca c 31

<210> SEQ ID NO 246
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 246

atggaagaag agaggtattc cccttcccac 30

<210> SEQ ID NO 247
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tggaagaaga gaggtattcc ccttcccac 29

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ggaagaagag aggtattccc cttcccac 28

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gaagaagaga ggtattcccc ttcccac 27

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aagaagagag gtattcccct tcccac 26

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agaagagagg tattcccctt cccac 25

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cctgagtcca gtttgccctc aagcccagat gc 32

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gagtccagtt tgccctcaag cccagatgc 29

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agtccagttt gccctcaagc ccagatgc 28

<210> SEQ ID NO 258

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gtccagtttg ccctcaagcc cagatgc 27

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tccagtttgc cctcaagccc agatgc 26

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cagtttgccc tcaagcccag atgc 24

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<220> FEATURE:
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<220> FEATURE:
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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 270

ccacagacct ggtccccaaa agaaatggag gcaatagg 38

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<212> TYPE: DNA

<213> ORGANISM: Artificial
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<400> SEQUENCE: 271

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<400> SEQUENCE: 272

acagacctgg tccccaaaag aaatggaggc aatagg 36

<210> SEQ ID NO 273
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<212> TYPE: DNA
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<400> SEQUENCE: 273

cagacctggt ccccaaaaga aatggaggca atagg 35

<210> SEQ ID NO 274
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<210> SEQ ID NO 276
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<400> SEQUENCE: 276

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<210> SEQ ID NO 277
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<212> TYPE: DNA
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<400> SEQUENCE: 277

cctggtcccc aaaagaaatg gaggcaatag g 31

<210> SEQ ID NO 278
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 278

ctggtcccca aaagaaatgg aggcaatagg 30

<210> SEQ ID NO 279
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<210> SEQ ID NO 280
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 282

tccccaaaag aaatggaggc aatagg 26

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

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<210> SEQ ID NO 284
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<223> OTHER INFORMATION: primer

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<220> FEATURE:
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<400> SEQUENCE: 285

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<210> SEQ ID NO 286
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 286

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<210> SEQ ID NO 287
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<212> TYPE: DNA
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<220> FEATURE:
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tctgggccac tgactgattt gtgtgtagga ccctgg 36

<210> SEQ ID NO 288
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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ctgggccact gactgatttg tgtgtaggac cctgg 35

<210> SEQ ID NO 289
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<212> TYPE: DNA
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ggccactgac tgatttgtgt gtaggaccct gg 32

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<212> TYPE: DNA
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<400> SEQUENCE: 292

gccactgact gatttgtgtg taggaccctg g 31

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 293

ccactgactg atttgtgtgt aggaccctgg 30

<210> SEQ ID NO 294
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<211> LENGTH: 28
<212> TYPE: DNA
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actgactgat ttgtgtgtag gaccctgg 28

<210> SEQ ID NO 296
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 296

ctgactgatt tgtgtgtagg accctgg 27

<210> SEQ ID NO 297
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 297

tgactgattt gtgtgtagga ccctgg 26

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 298

gactgatttg tgtgtaggac cctgg 25

<210> SEQ ID NO 299
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 299

actgatttgt gtgtaggacc ctgg 24

<210> SEQ ID NO 300
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ccaccccagc agcccccatt ctcctgctgc ctcacctggg ccccaggcag cagaaccagc 120

agcagcccca gaaggaggag gtgtagggtg gtgccacaca cccttgggag gaagagacgt 180

tcaggtggtg tcatggggag aacctgcaga gaaagagaga gagagagaga gacagtgagc 240

ggggcggggc acgcggcgga agacagacct cccgccctgg gagacagcac cccccgaccc 300

ccgagagaga gatcgacaga gaaggggaca agatgcagtc agagaaaccc caaggtgagc 360

agagggagac agagagagac aggaagggaa cagagaggaa ycatggcaga aacagagaat 420

gtgtgacaga gacaatgaga ctgacagatg gagagtcaga gacagagaag gaaaccaaaa 480

ccaaacccac caaggcccag gcccaggcag gccggggatc caggcagcag gtgcaggagg 540

gaccgaggcc caggcagagg gcaggacact gcggggcggt agtccaaagc acgaagcacg 600

ggcagcccaa ggagatgggg caggagagcc tcacctgctg tgtggagccc ctgggcccgg 660

acgctcaggt ccctttatag aggaagcggc agtggcagcg tggcaggcag cgggcgggtt 720

ctaggtcggg gctggggccc ggggaagccc ccagggctta gaagatactg ctgtttcagt 780

caaaggcagg aaaggctgag g 801

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<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 301

tgtttctgcc atggttcctc tc 22

<210> SEQ ID NO 302
<211> LENGTH: 21

<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 302

gtttctgcca tggttcctct c 21

<210> SEQ ID NO 303
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 303

tttctgccat ggttcctctc 20

<210> SEQ ID NO 304
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 304

ttctgccatg gttcctctc 19

<210> SEQ ID NO 305
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 305

tctgccatgg ttcctctc 18

<210> SEQ ID NO 306
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: probe

<400> SEQUENCE: 306

ctgccatggt tcctctc 17

<210> SEQ ID NO 307
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 307

tgccatggtt cctctc 16

<210> SEQ ID NO 308
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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 308

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gccatggttc ctctc 15

<210> SEQ ID NO 309
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 309

tttggtttcc ttctctgtct ctgactctcc atctgtc 37

<210> SEQ ID NO 310
<211> LENGTH: 36
<212> TYPE: DNA
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<400> SEQUENCE: 310

ttggtttcct tctctgtctc tgactctcca tctgtc 36

<210> SEQ ID NO 311
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 311

tggtttcctt ctctgtctct gactctccat ctgtc 35

<210> SEQ ID NO 312
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 312

ggtttccttc tctgtctctg actctccatc tgtc 34

<210> SEQ ID NO 313
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 313

gtttccttct ctgtctctga ctctccatct gtc 33

<210> SEQ ID NO 314
<211> LENGTH: 32
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 314

tttccttctc tgtctctgac tctccatctg tc 32

<210> SEQ ID NO 315
<211> LENGTH: 31
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 315

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<210> SEQ ID NO 316
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 316

tccttctctg tctctgactc tccatctgtc 30

<210> SEQ ID NO 317
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 317

ccttctctgt ctctgactct ccatctgtc 29

<210> SEQ ID NO 318
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 318

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<210> SEQ ID NO 319
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 319

ttctctgtct ctgactctcc atctgtc 27

<210> SEQ ID NO 320
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<210> SEQ ID NO 321
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 321

ctctgtctct gactctccat ctgtc 25

<210> SEQ ID NO 322
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 322

tctgtctctg actctccatc tgtc 24

<210> SEQ ID NO 323
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 323

ctgtctctga ctctccatct gtc 23

<210> SEQ ID NO 324
<211> LENGTH: 22
<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 324

tgtctctgac tctccatctg tc 22

<210> SEQ ID NO 325
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 325

gtctctgact ctccatctgt c 21

<210> SEQ ID NO 326
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 326

tctctgactc tccatctgtc 20

<210> SEQ ID NO 327
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 327

ctctgactct ccatctgtc 19

<210> SEQ ID NO 328
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 328

tctgactctc catctgtc 18

<210> SEQ ID NO 329
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 329

ctgactctcc atctgtc 17

<210> SEQ ID NO 330
<211> LENGTH: 37
<212> TYPE: DNA
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<400> SEQUENCE: 330

cgacagagaa ggggacaaga tgcagtcaga gaaaccc 37

<210> SEQ ID NO 331
<211> LENGTH: 36
<212> TYPE: DNA
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<400> SEQUENCE: 331

gacagagaag gggacaagat gcagtcagag aaaccc 36

<210> SEQ ID NO 332
<211> LENGTH: 35
<212> TYPE: DNA
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<400> SEQUENCE: 332

acagagaagg ggacaagatg cagtcagaga aaccc 35

<210> SEQ ID NO 333
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<212> TYPE: DNA
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<400> SEQUENCE: 333

cagagaaggg gacaagatgc agtcagagaa accc 34

<210> SEQ ID NO 334
<211> LENGTH: 33
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 334

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<210> SEQ ID NO 335

<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 335

gagaagggga caagatgcag tcagagaaac cc 32

<210> SEQ ID NO 336
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 336

agaaggggac aagatgcagt cagagaaacc c 31

<210> SEQ ID NO 337
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 337

gaaggggaca agatgcagtc agagaaaccc 30

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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 338

aaggggacaa gatgcagtca gagaaaccc 29

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aggggacaag atgcagtcag agaaaccc 28

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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 340

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<210> SEQ ID NO 341
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 341

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aagatgcagt cagagaaacc c 21

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agatgcagtc agagaaaccc 20

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<213> ORGANISM: Artificial
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gatgcagtca gagaaaccc 19

<210> SEQ ID NO 349
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 349

atgcagtcag agaaaccc 18

The invention claimed is:

1. A polymorphism detection probe consisting of oligonucleotide (A) and at least one fluorescent dye bonded to said oligonucleotide (A),

wherein the oligonucleotide (A) consists of the nucleotide sequence of SEQ ID NO: 14 or the complementary sequence thereof.

2. The polymorphism detection probe according to claim **1**, wherein the probe does not emit fluorescence when alone and emits fluorescence when forming a hybrid.

3. The polymorphism detection probe according to claim **1**, wherein the probe emits fluorescence when alone and emits reduced fluorescence when forming a hybrid.

4. The polymorphism detection probe according to claim **1**, wherein the at least one fluorescent dye is bonded to the cytosine at the 3' end of the oligonucleotide (A).

5. A polymorphism detection reagent for detecting a polymorphism of an immune-related gene, comprising the polymorphism detection probe of claim **1**.

6. A method of detecting a polymorphism in a FCGR3A gene, comprising:

hybridizing a sample nucleic acid and the polymorphism detection probe of claim **1**,

measuring a fluorescence signal value that indicates the melting state of one or more products of the hybridization in a reaction system while changing the temperature of the reaction system; and

determining the polymorphism in the sample nucleic acid based on a change in the fluorescence signal value associated with the temperature change.

7. The method of detecting a polymorphism according to claim **6**, wherein

the method comprises:

generating in the reaction system an amplification product that serves as the sample nucleic acid.

8. The polymorphism detection probe according to claim **1**, wherein the oligonucleotide (A) consists of the nucleotide sequence of SEQ ID NO: 14.

9. The polymorphism detection probe according to claim **1**, wherein the fluorescent dye is selected from the group consisting of fluoresceins, phosphors, rhodamine, and polymethine dye.

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